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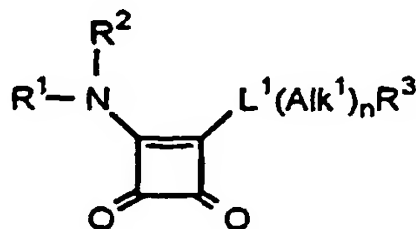
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(54) Title: SQUARIC ACID DERIVATIVES AS CELL ADHESION MOLECULES



(1)

(57) Abstract: Squaric acid Derivatives of formula  
(1) are described: wherein R<sup>1</sup> is an integrin  
binding group; R<sup>2</sup> is a hydrogen atom or a C<sub>1-6</sub>  
alkyl group; L<sup>1</sup> is a covalent bond or a linker  
atom or group; n is zero or the integer 1; Alk<sup>1</sup>  
is an optionally substituted aliphatic chain; R<sup>3</sup>  
is a hydrogen atom or an optionally substituted  
heteroaliphatic, cycloaliphatic, heterocycloaliphatic,  
polycycloaliphatic, polyheterocycloaliphatic,  
aromatic or heteroaromatic group: and the salts,  
solvates, hydrates and N-oxides thereof. The

compounds are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or  
inflammatory disorders, or disorders involving the inappropriate growth or migration of cells.

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## SQUARIC ACID DERIVATIVES AS CELL ADHESION MOLECULES

This invention relates to a series of squaric acid derivatives, to compositions containing them, to processes for their preparation, and to  
5 their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory  
10 responses [Springer, T A. Nature, 346, 425, (1990); Springer, T. A. Cell 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

The adhesion molecules have been sub-divided into different groups on  
15 the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At  
20 least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. Current Topics in Microbiology and Immunology, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial  
nomenclature is widespread in this field. Thus the integrin termed  $\alpha 4\beta 1$  consists of the integrin alpha 4 chain associated with the integrin beta 1  
25 chain, but is also widely referred to as Very Late Antigen 4 or VLA4.

Some integrin chains are capable of pairing with more than one partner. For example, the  $\alpha_v$  chain has been reported to pair with the beta 1 chain, the beta 3 chain, the beta 5 chain, the beta 6 chain and the beta 8 chain to  
30 give molecules which bind to different sets of ligands and which are referred to respectively as the integrins  $\alpha_v\beta_1$ ,  $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$ ,  $\alpha_v\beta_6$ , and  $\alpha_v\beta_8$ . Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a  
number of subgroups based on the pairings that have been recognised  
35 [Sonnenberg, A. *ibid*].

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is defective. Thus in the disease termed Leukocyte Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed [on  
5 leukocytes. Patients suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integer famly) there is a defect in blood clotting.

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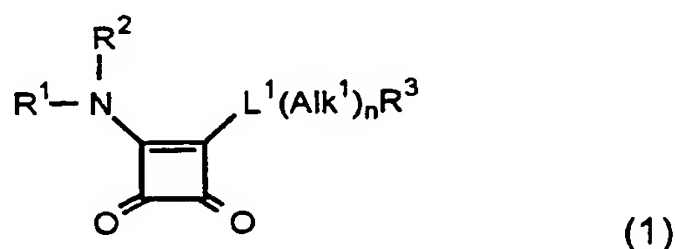
The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific monoclonal antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol.  
15 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Mitjans *et al* J. Cell Sci. 108, 2825 (1995), Brooks P.C. *et al* J.Clin. Invest. 96, 1815 (1995), Binns, R. M. *et al* J. Immunol. 157, 4094, (1996), Hammes, H-P, *et al* Nature Medicine 2, 529 (1996), Srivata, S. *et al* Cardiovascular Res. 36, 408 (1997)]. A number of monoclonal antibodies which block integrin  
20 function are currently being investigated for their therapeutic potential in human disease.

Inhibition of integrin-mediated cell interaction can be expected to be beneficial in a number of disease states, and in addition to the monoclonal  
25 antibodies and peptides just mentioned there has been great interest in selective low molecular weight inhibitors of integrin function. Thus, for example selective  $\alpha_4$  integrin inhibitors have been described in International patent Specifications Nos. WO96/22966, WO97/03094, WO  
98/04247, WO98/04913, WO98/53814, WO98/53817, WO98/53818,  
30 WO98/54207, WO98/58902, WO99/06390, WO99/06431-06437, WO99/10312, WO99/10313, WO99/67230, WO 99/26922, WO99/60015, WO99/26921, WO9936393, WO99/52898 and WO99/64395. Numerous selective  $\alpha_v$  integrin inhibitors have also been described, for example in International Patent Specifications Nos. WO97/08145, WO97/23480,  
35 WO97/36858, WO97/36859, WO97/36861, WO97/36862, WO97/44333, WO97/47618, WO98/31359, WO98/25892, WO98/18460, WO99/44994,

WO99/30709, WO99/31061, WO 99/26945, WO99/52896, WO99/52879, WO99/32457, WO99/31099, WO00/07544, WO00/00486, WO00/06169, WO00/17197 and WO00/01383.

- 5 While it is clearly possible to obtain selective integrin inhibitors, their usefulnesses in medicine may be limited due to poor pharmacokinetic properties. Thus, for example, in our hands, integrin inhibitors falling within the general structural types featured in the above-mentioned patent specifications are not particularly attractive for development as medicines  
 10 since they can be cleared rapidly from the body. In order to overcome this problem we have made use of a squaric acid framework which can be readily adapted to provide potent and selective integrin inhibitors using recognised integrin binding groups (for example as described herein and in the patent specifications listed above), which advantageously possess  
 15 good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)



wherein

R<sup>1</sup> is an integrin binding group;

R<sup>2</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl group;

25 L<sup>1</sup> is a covalent bond or a linker atom or group;

n is zero or the integer 1;

Alk<sup>1</sup> is an optionally substituted aliphatic chain;

R<sup>3</sup> is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocyclo-  
 30 aliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.



It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

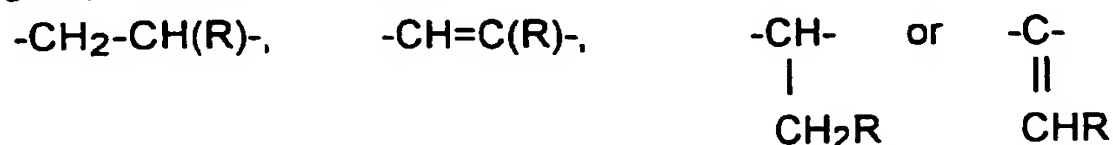
In the compounds according to the invention, integrin-binding groups represented by  $R^1$  include for example those which are able to bind  $\alpha_4$ - or  $\alpha_v$ -integrins. Particular examples of such integrins include  $\alpha_4\beta_1$ ,  $\alpha_4\beta_7$  and  $\alpha_v\beta_3$  integrins.

In general, the term integrin-binding group is used herein in relation to  $R^1$  to mean any group which when part of the compound of formula (1) is able to interact with an integrin to modulate cell adhesion *in vivo* and achieve a therapeutic response. Typically the  $R^1$  group may bind to the integrin in such a way that it modulates the interaction of the integrin with its ligand. Thus for example the  $R^1$  group may inhibit binding of the ligand and decrease cell adhesion. Such a response enables appropriate  $R^1$  groups to be readily identified using small scale routine *in vitro* screening assays to determine the degree of inhibition of integrin-ligand binding in the presence of a compound of formula (1). Examples of such screening assays are widely reported in the literature, for example in the papers and International patent specifications described above, and in the Examples hereinafter.

Thus in general  $R^1$  may be any group which when present in a compound of formula (1) is able to bind to an integrin such that the compound of formula (1) inhibits the binding of the integrin with its ligand with an  $IC_{50}$  of  $10\mu M$  or below, particularly  $1\mu M$  or below, especially  $500nM$  or below, e.g. in the range  $0.001 - 500nM$ .

Particular  $R^1$  groups in compounds of the invention include those of formula  $Ar^1L^2Ar^2Alk$ - wherein  $Ar^1$  is an optionally substituted aromatic or heteroaromatic group,  $L^2$  is a linker atom or group,  $Ar^2$  is an optionally

substituted phenylene or nitrogen-containing six-membered heteroarylene group and Alk is a chain:



where R is a carboxylic acid (-CO<sub>2</sub>H) or a derivative or biostere thereof.

R<sup>1</sup> groups of this type are particularly useful for binding α<sub>4</sub> integrins and compounds of formula (1) incorporating the Ar<sup>1</sup>L<sup>2</sup>Ar<sup>2</sup>Alk- function can be expected to inhibit α<sub>4</sub> integrins such as α<sub>4</sub>β<sub>1</sub> and/or α<sub>4</sub>β<sub>7</sub> at concentrations at which they generally have no or minimal inhibitory action on integrins of other α subgroups. Such compounds are of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

Optionally substituted aromatic groups represented by Ar<sup>1</sup> when present in the group R<sup>1</sup> include for example optionally substituted monocyclic or bicyclic fused ring C<sub>6-12</sub> aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups represented by the group Ar<sup>1</sup> when present in the group R<sup>1</sup> include for example optionally substituted C<sub>1-9</sub> heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C<sub>1-6</sub>alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl,

1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, 5 benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, especially 2,6-naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and 10 imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group  $Ar^1$  may be optionally substituted on any available carbon or, when present, 15 nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group  $-L^3(Alk^2)_tL^4(R^4)_u$  in which  $L^3$  and  $L^4$ , which may be the same or different, is each a covalent bond or a linker atom or group,  $t$  is zero or the integer 1,  $u$  is an integer 1, 2 or 3,  $Alk^2$  is an 20 aliphatic or heteroaliphatic chain and  $R^4$  is a hydrogen or halogen atom or a group selected from optionally substituted  $C_{1-6}$ alkyl or  $C_{3-8}$  cycloalkyl,  $-OR^5$  [where  $R^5$  is a hydrogen atom, an optionally substituted  $C_{1-6}$ alkyl or  $C_{3-8}$  cycloalkyl group],  $-SR^5$ ,  $-NR^5R^6$  [where  $R^6$  is as just defined for  $R^5$  and may be the same or different],  $-NO_2$ ,  $-CN$ ,  $-CO_2R^5$ ,  $-SO_3H$ ,  $-SOR^5$ , 25  $-SO_2R^5$ ,  $-SO_3R^5$ ,  $-OCO_2R^5$ ,  $-CONR^5R^6$ ,  $-OCONR^5R^6$ ,  $-CSNR^5R^6$ ,  $-COR^5$ ,  $-OCOR^5$ ,  $-N(R^5)COR^6$ ,  $-N(R^5)CSR^6$ ,  $-SO_2N(R^5)(R^6)$ ,  $-N(R^5)SO_2R^6$ ,  $N(R^5)CON(R^6)(R^7)$  [where  $R^7$  is a hydrogen atom, an optionally substituted  $C_{1-6}$ alkyl or  $C_{3-8}$ cycloalkyl group],  $-N(R^5)CSN(R^6)(R^7)$  or  $-N(R^5)SO_2N(R^6)(R^7)$ , provided that when  $t$  is zero and each of  $L^3$  and  $L^4$  is a covalent bond then  $u$  is the integer 1 and  $R^4$  is 30 other than a hydrogen atom.

When  $L^3$  and/or  $L^4$  is present in these substituents as a linker atom or group it may be any divalent linking atom or group. Particular examples 35 include  $-O-$  or  $-S-$  atoms or  $-C(O)-$ ,  $-C(O)O-$ ,  $-OC(O)-$ ,  $-C(S)-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-N(R^8)-$  [where  $R^8$  is a hydrogen atom or an optionally

substituted C<sub>1-6</sub>alkyl group], -N(R<sup>8</sup>)O-, -N(R<sup>8</sup>)N-, -CON(R<sup>8</sup>)-,  
 -OC(O)N(R<sup>8</sup>)-, -CSN(R<sup>8</sup>)-, -N(R<sup>8</sup>)CO-, -N(R<sup>8</sup>)C(O)O-, -N(R<sup>8</sup>)CS-,  
 -S(O)<sub>2</sub>N(R<sup>8</sup>)-, -N(R<sup>8</sup>)S(O)<sub>2</sub>-, -N(R<sup>8</sup>)CON(R<sup>8</sup>)-, -N(R<sup>8</sup>)CSN(R<sup>8</sup>)-, or  
 -N(R<sup>8</sup>)SO<sub>2</sub>N(R<sup>8</sup>)- groups. Where the linker group contains two R<sup>8</sup>  
 5 substituents, these may be the same or different.

When R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and/or R<sup>8</sup> is present as a C<sub>1-6</sub>alkyl group it may be  
 a straight or branched C<sub>1-6</sub>alkyl group, e.g. a C<sub>1-3</sub>alkyl group such as a  
 methyl or ethyl group. C<sub>3-8</sub>cycloalkyl groups represented by R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>  
 10 and/or R<sup>8</sup> include C<sub>3-6</sub>cycloalkyl groups e.g. cyclopropyl, cyclobutyl,  
 cyclopentyl and cyclohexyl groups. Optional substituents which may be  
 present on such alkyl and cycloalkyl groups include for example one, two  
 or three substituents which may be the same or different selected from  
 halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or  
 15 hydroxy or C<sub>1-6</sub>alkoxy e.g. methoxy or ethoxy groups.

When the groups R<sup>5</sup> and R<sup>6</sup> or R<sup>6</sup> and R<sup>7</sup> are both C<sub>1-6</sub>alkyl groups these  
 groups may be joined, together with the N atom to which they are  
 attached, to form a heterocyclic ring. Such heterocyclic rings may be  
 20 optionally interrupted by a further heteroatom selected from -O-, -S- or  
 -N(R<sup>5</sup>)-. Particular examples of such heterocyclic rings include piperidiny,  
 morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl  
 rings.

25 When Alk<sup>2</sup> is present as an aliphatic or heteroaliphatic chain it may be for  
 example any divalent chain corresponding to the below-mentioned  
 aliphatic or heteroaliphatic group described for Alk<sup>1</sup> or R<sup>3</sup> respectively.

Halogen atoms represented by R<sup>4</sup> in the optional Ar<sup>1</sup> substituents include  
 30 fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by -L<sup>3</sup>(Alk<sup>2</sup>)<sub>t</sub>L<sup>4</sup>(R<sup>4</sup>)<sub>u</sub> when  
 present in Ar<sup>1</sup> groups in compounds of the invention include atoms or  
 groups -L<sup>3</sup>Alk<sup>2</sup>L<sup>4</sup>R<sup>4</sup>, -L<sup>3</sup>Alk<sup>2</sup>R<sup>4</sup>, -L<sup>3</sup>R<sup>4</sup>, -R<sup>4</sup> and -Alk<sup>2</sup>R<sup>4</sup> wherein L<sup>3</sup>, Alk<sup>2</sup>,  
 35 L<sup>4</sup> and R<sup>4</sup> are as defined above. Particular examples of such substituents  
 include -L<sup>3</sup>CH<sub>2</sub>L<sup>4</sup>R<sup>4</sup>, -L<sup>3</sup>CH(CH<sub>3</sub>)L<sup>4</sup>R<sup>4</sup>, -L<sup>3</sup>CH(CH<sub>2</sub>)<sub>2</sub>L<sup>4</sup>R<sup>4</sup>, -L<sup>3</sup>CH<sub>2</sub>R<sup>4</sup>,

$-L^3CH(CH_3)R^4$ ,  $-L^3(CH_2)_2R^4$ ,  $-CH_2R^4$ ,  $-CH(CH_3)R^4$ ,  $-(CH_2)_2R^4$  and  $-R^4$  groups.

Thus  $Ar^1$  in compounds of the invention may be optionally substituted for  
 5 example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or  $C_{1-6}$ alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl,  $C_{3-8}$ cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl,  $C_{1-6}$ hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or  $-C(OH)(CF_3)_2$ , carboxy $C_{1-6}$ alkyl, e.g. carboxyethyl,  $C_{1-6}$ alkylthio e.g. methylthio or ethylthio, carboxy $C_{1-6}$ alkylthio, e.g.  
 10 carboxymethylthio, 2-carboxyethylthio or 3-carboxy-propylthio,  $C_{1-6}$ alkoxy, e.g. methoxy or ethoxy, hydroxy $C_{1-6}$ alkoxy, e.g. 2-hydroxyethoxy, halo $C_{1-6}$ alkyl, e.g.  $-CF_3$ ,  $-CHF_2$ ,  $CH_2F$ , halo $C_{1-6}$ alkoxy, e.g.  $-OCF_3$ ,  $-OCHF_2$ ,  $-OCH_2F$ ,  $C_{1-6}$ alkylamino, e.g. methylamino or ethylamino, amino ( $-NH_2$ ),  
 15 amino $C_{1-6}$ alkyl, e.g. aminomethyl or aminoethyl,  $C_{1-6}$ dialkylamino, e.g. dimethylamino or diethylamino,  $C_{1-6}$ alkylamino $C_{1-6}$ alkyl, e.g. ethylaminoethyl,  $C_{1-6}$ dialkylamino $C_{1-6}$ alkyl, e.g. diethylaminoethyl, amino $C_{1-6}$ alkoxy, e.g. aminoethoxy,  $C_{1-6}$ alkylamino $C_{1-6}$ alkoxy, e.g. methylaminoethoxy,  $C_{1-6}$ dialkylamino $C_{1-6}$ alkoxy, e.g. dimethylamino-  
 20 ethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylamino-propoxy, nitro, cyano, amidino, hydroxyl ( $-OH$ ), formyl [ $HC(O)-$ ], carboxyl ( $-CO_2H$ ),  $-CO_2Alk^3$  [where  $Alk^3$  is as defined below for  $Alk^7$ ],  $C_{1-6}$ alkanoyl e.g. acetyl, thiol ( $-SH$ ), thio $C_{1-6}$ alkyl, e.g. thiomethyl or thioethyl, sulphonyl ( $-SO_3H$ ),  $-SO_3Alk^3$ ,  $C_{1-6}$ alkylsulphonyl, e.g. methylsulphonyl,  $C_{1-6}$ alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ( $-SO_2NH_2$ ),  $C_{1-6}$ alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl,  $C_{1-6}$ dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylamino-  
 25 sulphonyl, phenylaminosulphonyl, carboxamido ( $-CONH_2$ ),  $C_{1-6}$ alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl,  $C_{1-6}$ dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylamino-carbonyl, amino $C_{1-6}$ alkylaminocarbonyl, e.g. aminoethylaminocarbonyl,  $C_{1-6}$ dialkylamino $C_{1-6}$ alkylaminocarbonyl, e.g. diethylaminoethylamino-carbonyl, aminocarbonylamino,  $C_{1-6}$ alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino,  $C_{1-6}$ dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylamino-  
 30 carbonylamino,  $C_{1-6}$ alkylaminocarbonyl $C_{1-6}$ alkylamino, e.g. methylamino-

carbonylmethylamino, aminothiocabonylamino, C<sub>1-6</sub>alkylaminothio-  
carbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothio-  
carbonylamino, C<sub>1-6</sub>dialkylaminothiocarbonylamino, e.g. dimethylamino-  
thiocarbonylamino or diethylaminothiocarbonylamino, C<sub>1-6</sub>alkylamino-  
5 thiocarbonylC<sub>1-6</sub>alkylamino, e.g. ethylaminothiocarbonylmethylamino, C<sub>1-6</sub>  
alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino,  
C<sub>1-6</sub>dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethyl-  
sulphonylamino, aminosulphonylamino (-NHSO<sub>2</sub>NH<sub>2</sub>), C<sub>1-6</sub>alkylamino-  
sulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonyl-  
10 amino, C<sub>1-6</sub>dialkylaminosulphonylamino, e.g. dimethylaminosulphonyl-  
amino or diethylaminosulphonylamino, C<sub>1-6</sub>alkanoylamino, e.g.  
acetylamino, aminoC<sub>1-6</sub>alkanoylamino e.g. aminoacetylamino, C<sub>1-6</sub>  
dialkylaminoC<sub>1-6</sub>alkanoylamino, e.g. dimethylaminoacetylamino, C<sub>1-6</sub>  
alkanoylaminoC<sub>1-6</sub>alkyl, e.g. acetylaminomethyl, C<sub>1-6</sub>alkanoylaminoC<sub>1-6</sub>  
15 6alkylamino, e.g. acetamidoethylamino, C<sub>1-6</sub>alkoxycarbonylamino, e.g.  
methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino  
groups.

L<sup>2</sup> when present as part of the group R<sup>1</sup> in compounds of the invention  
20 may be a linker atom or group L<sup>2a</sup> or a linker -Alk<sup>a</sup>(L<sup>2a</sup>)<sub>y</sub>-, where Alk<sup>a</sup> is an  
optionally substituted aliphatic or heteroaliphatic chain as previously  
defined for Alk<sup>2</sup>, and L<sup>2a</sup> is a linker atom or group as described above for  
L<sup>3</sup> and L<sup>4</sup> and y is zero or the integer 1.

25 Optionally substituted nitrogen-containing six-membered heteroarylene  
groups represented by Ar<sup>2</sup> when present as part of the group R<sup>1</sup> include  
optionally substituted pyridyl, pyrimidindyl, pyridazindyl, pyrazindyl and  
triazindyl groups. Each group may be attached to the remainder of the  
molecule through any available ring carbon atoms.

30 The phenylene and nitrogen-containing heteroarylene groups represented  
by Ar<sup>2</sup> may be optionally substituted by one or two substituents selected  
from the atoms or groups -L<sup>3</sup>(Alk<sup>2</sup>)<sub>t</sub>L<sup>4</sup>(R<sup>4</sup>)<sub>u</sub> described herein. Where two  
of these atoms or groups are present they may be the same or different.

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When the group R is present in R<sup>1</sup> in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include -CO<sub>2</sub>Alk<sup>7</sup> and -CONR<sup>5</sup>R<sup>6</sup> groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

When the group R<sup>2</sup> is present in compounds of the invention as a C<sub>1-6</sub>alkyl group it may be for example a straight or branched C<sub>1-6</sub>alkyl group, e.g. a C<sub>1-3</sub>alkyl group such as a methyl or ethyl group.

The linker atom or group represented by L<sup>1</sup> in compounds of formula (1) may be any linker atom or group as described above for the linker atom or group L<sup>3</sup>.

When the group Alk<sup>1</sup> is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C<sub>1-10</sub> aliphatic chain. Particular examples include optionally substituted straight or branched chain C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkenylene, or C<sub>2-6</sub> alkynylene chains.

Particular examples of aliphatic chains represented by Alk<sup>1</sup> include optionally substituted -CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>2</sub>-, -CHCH-, -CHCHCH<sub>2</sub>-, -CH<sub>2</sub>CHCH-, -CHCHCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CHCHCH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>2</sub>CHCH-, -CC-, -CCCH<sub>2</sub>-, -CH<sub>2</sub>CC-, -CCCH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CCCH<sub>2</sub>- or -(CH<sub>2</sub>)<sub>2</sub>CCH- groups.

Heteroaliphatic groups represented by the group R<sup>3</sup> in the compounds of formula (1) include the aliphatic chains just described for Alk<sup>1</sup> but with each containing a terminal hydrogen atom and additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L<sup>5</sup> where L<sup>5</sup> is as defined above for L<sup>3</sup> when L<sup>3</sup> is a linker atom or group. Each L<sup>5</sup> atom or group



may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted  $-L^5CH_3$ ,  $-CH_2L^5CH_3$ ,  $-L^5CH_2CH_3$ ,  $-CH_2L^5CH_2CH_3$ ,  $-(CH_2)_2L^5CH_3$ ,  $-(CH_2)_3L^5CH_3$ ,  $-L^5(CH_2)_3$ ,  
5 and  $-(CH_2)_2L^5CH_2CH_3$  groups.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by  $Alk^1$  and  $R^3$  respectively include one, two, three or more substituents where each substituent may be the  
10 same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or  $-OH$ ,  $-CO_2H$ ,  $-CO_2R^9$ , where  $R^9$  is an optionally substituted straight or branched  $C_{1-6}$ alkyl group as defined above for  $R^4$ ,  $-CONHR^9$ ,  $-CON(R^a)_2$ ,  $-COCH_3$ ,  $C_{1-6}$ alkoxy, e.g. methoxy or ethoxy, thiol,  $-S(O)R^9$ ,  $-S(O)_2R^9$ ,  $C_{1-6}$ alkylthio e.g. methylthio or  
15 ethylthio, amino or substituted amino groups. Substituted amino groups include  $-NHR^9$  and  $-N(R^9)_2$  groups. Where two  $R^9$  groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group  $R^3$  in  
20 compounds of the invention include optionally substituted  $C_{3-10}$  cycloaliphatic groups. Particular examples include optionally substituted  $C_{3-10}$  cycloalkyl, e.g.  $C_{3-7}$  cycloalkyl or  $C_{3-10}$  cycloalkenyl, e.g.  $C_{3-7}$  cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group  $R^3$  include optionally substituted  $C_{3-10}$ heterocycloaliphatic groups. Particular examples include optionally substituted  $C_{3-10}$ heterocycloalkyl, e.g.  $C_{3-7}$  heterocycloalkyl, or  $C_{3-10}$ heterocycloalkenyl, e.g.  $C_{3-7}$  heterocycloalkenyl groups, each of said groups containing one, two, three  
25 or four heteroatoms or heteroatom-containing groups  $L^5$  as defined above.  
30

Optionally substituted polycycloaliphatic groups represented by the group  $R^3$  include optionally substituted  $C_{7-10}$  bi- or tricycloalkyl or  $C_{7-10}$ bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic  
35 groups represented by the group  $R^3$  include the optionally substituted

polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L<sup>5</sup> atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups represented by the group R<sup>3</sup> include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups represented by the group R<sup>3</sup> include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C<sub>1-6</sub>alkyl, e.g. methyl or ethyl, haloC<sub>1-6</sub>alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF<sub>3</sub>)<sub>2</sub>, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, haloC<sub>1-6</sub>alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C<sub>1-6</sub>alkylthio e.g. methylthio or ethylthio, or -(Alk<sup>4</sup>)<sub>v</sub>R<sup>10</sup> groups in which Alk<sup>4</sup> is a straight or branched C<sub>1-3</sub>alkylene chain, v is zero or an integer 1 and R<sup>10</sup> is a -OH, -SH, -N(R<sup>11</sup>)<sub>2</sub>, (in which R<sup>11</sup> is an atom or group as defined herein for R<sup>8</sup>) -CN, -CO<sub>2</sub>R<sup>11</sup>, -NO<sub>2</sub>, -CON(R<sup>11</sup>)<sub>2</sub>, -CSN(R<sup>11</sup>)<sub>2</sub>, -COR<sup>11</sup>, -CSN(R<sup>11</sup>)<sub>2</sub>, -N(R<sup>11</sup>)COR<sup>11</sup>, -N(R<sup>11</sup>)CSR<sup>11</sup>, -SO<sub>2</sub>N(R<sup>11</sup>)<sub>2</sub>, -N(R<sup>11</sup>)SO<sub>2</sub>R<sup>11</sup>, -N(R<sup>11</sup>)CON(R<sup>11</sup>)<sub>2</sub>, -N(R<sup>11</sup>)CSN(R<sup>11</sup>), N(R<sup>11</sup>)SO<sub>2</sub>N(R<sup>11</sup>)<sub>2</sub> or optionally substituted phenyl group. Where two R<sup>11</sup> atoms or groups are present in these substituents these may be the same or different. Optionally substituted phenyl groups include phenyl substituted by one, two or three of the R<sup>13</sup> groups described below

Additionally, when the group  $R^3$  is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group  $-(L^6)_p(Alk^5)_qR^{12}$  in which  $L^6$  is  $-C(O)-$ ,  $-C(O)O-$ ,  $-C(S)-$ ,  $-S(O)_2-$ ,  $-CON(R^{11})-$ ,  $-CSN(R^{11})-$  or  $SO_2N(R^{11})-$ ;  $p$  is zero or an integer 1;  $Alk^5$  is an optionally substituted aliphatic or heteroaliphatic chain;  $q$  is zero or an integer 1; and  $R^{12}$  is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

10

Optionally substituted aliphatic or heteroaliphatic chains represented by  $Alk^5$  include those optionally substituted chains described above for  $Alk^1$  and  $R^3$  respectively.

15

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by  $R^{12}$  include those groups just described for the group  $R^3$ . Optional substituents which may be present on these groups include those described above in relation to  $Alk^1$  and  $R^3$  aliphatic and heteroaliphatic chains.

20

When the group  $R^3$  is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group  $Ar^1$ .

25

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group  $R^3$  include one, two, three or more substituents, each selected from an atom or group  $R^{13}$  in which  $R^{13}$  is  $-R^{13a}$  or  $-Alk^6(R^{13a})_m$ , where  $R^{13a}$  is a halogen atom, or an amino ( $-NH_2$ ), substituted amino, nitro, cyano, amidino, hydroxyl ( $-OH$ ), substituted hydroxyl, formyl, carboxyl ( $-CO_2H$ ), esterified carboxyl, thiol ( $-SH$ ), substituted thiol,  $-COR^{14}$  [where  $R^{14}$  is an  $-Alk^6(R^{13a})_m$ , cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group],  $-CSR^{14}$ ,  $-SO_3H$ ,  $-SOR^{14}$ ,  $-SO_2R^{14}$ ,  $-SO_3R^{14}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{14}$ ,  $SO_2N(R^{14})_2$ ,  $-CONH_2$ ,  $-CSNH_2$ ,  $-CONHR^{14}$ ,  $-CSNHR^{14}$ ,  $-CON[R^{14}]_2$ ,  $-CSN(R^{14})_2$ ,  $-N(R^{11})SO_2R^{14}$ ,  $-N(SO_2R^{14})_2$ ,  $-NH(R^{11})SO_2NH_2$ ,  $-N(R^{11})SO_2NHR^{14}$ ,  $-N(R^{11})SO_2N(R^{14})_2$ ,  $-N(R^{11})COR^{14}$ ,  $-N(R^{11})CONH_2$ ,  $-N(R^{11})CONHR^{14}$ ,

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-N(R<sup>11</sup>)CON(R<sup>14</sup>)<sub>2</sub>, -N(R<sup>11</sup>)CSNH<sub>2</sub>, -N(R<sup>11</sup>)CSNHR<sup>14</sup>, -N(R<sup>11</sup>)CSN(R<sup>14</sup>)<sub>2</sub>,  
 -N(R<sup>11</sup>)CSR<sup>14</sup>, -N(R<sup>11</sup>)C(O)OR<sup>14</sup>, -SO<sub>2</sub>NHet<sup>1</sup> [where -NHet<sup>1</sup> is an  
 optionally substituted C<sub>5-7</sub>cyclicamino group optionally containing one or  
 more other -O- or -S- atoms or -N(R<sup>11</sup>)-, -C(O)-, -C(S)-, S(O) or -S(O)<sub>2</sub>  
 5 groups], -CONHet<sup>1</sup>, -CSNHet<sup>1</sup>, -N(R<sup>11</sup>)SO<sub>2</sub>NHet<sup>1</sup>, -N(R<sup>11</sup>)CONHet<sup>1</sup>,  
 -N(R<sup>11</sup>)CSNHet<sup>1</sup>, -SO<sub>2</sub>N(R<sup>11</sup>)Het<sup>2</sup> [where Het<sup>2</sup> is an optionally substituted  
 monocyclic C<sub>5-7</sub>carbocyclic group optionally containing one or more -O- or  
 -S- atoms or -N(R<sup>11</sup>)-, -C(O)- or -C(S)- groups], -Het<sup>2</sup>, -CON(R<sup>11</sup>)Het<sup>2</sup>,  
 -CSN(R<sup>11</sup>)Het<sup>2</sup>, -N(R<sup>11</sup>)CON(R<sup>11</sup>)Het<sup>2</sup>, -N(R<sup>11</sup>)CSN(R<sup>11</sup>)Het<sup>2</sup>, cyclo-  
 10 aliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk<sup>6</sup> is a straight or  
 branched C<sub>1-6</sub>alkylene, C<sub>2-6</sub>alkenylene or C<sub>2-6</sub>alkynylene chain, optionally  
 interrupted by one, two or three -O- or -S- atoms or -S(O)<sub>n</sub> [where n is an  
 integer 1 or 2] or -N(R<sup>15</sup>)- groups [where R<sup>15</sup> is a hydrogen atom or C<sub>1-6</sub>  
 alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It  
 15 will be appreciated that when two R<sup>11</sup> or R<sup>14</sup> groups are present in one of  
 the above substituents, the R<sup>11</sup> or R<sup>14</sup> groups may be the same or  
 different.

When in the group -Alk<sup>6</sup>(R<sup>13a</sup>)<sub>m</sub> m is an integer 1, 2 or 3, it is to be  
 20 understood that the substituent or substituents R<sup>13a</sup> may be present on  
 any suitable carbon atom in -Alk<sup>6</sup>. Where more than one R<sup>13a</sup> substituent  
 is present these may be the same or different and may be present on the  
 same or different atom in -Alk<sup>6</sup>. Clearly, when m is zero and no  
 substituent R<sup>13a</sup> is present the alkylene, alkenylene or alkynylene chain  
 25 represented by Alk<sup>6</sup> becomes an alkyl, alkenyl or alkynyl group.

When R<sup>13a</sup> is a substituted amino group it may be for example a group  
 -NHR<sup>14</sup> [where R<sup>14</sup> is as defined above] or a group -N(R<sup>14</sup>)<sub>2</sub> wherein each  
 R<sup>14</sup> group is the same or different.

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When R<sup>13a</sup> is a halogen atom it may be for example a fluorine, chlorine,  
 bromine, or iodine atom.

When R<sup>13a</sup> is a substituted hydroxyl or substituted thiol group it may be for  
 35 example a group -OR<sup>14</sup> or a -SR<sup>14</sup> or -SC(=NH)NH<sub>2</sub> group respectively.

Esterified carboxyl groups represented by the group  $R^{13a}$  include groups of formula  $-CO_2Alk^7$  wherein  $Alk^7$  is a straight or branched, optionally substituted  $C_{1-8}$ alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a  $C_{6-12}$ aryl $C_{1-8}$ alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a  $C_{6-12}$ aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a  $C_{6-12}$ aryloxy $C_{1-8}$ alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted  $C_{1-8}$ alkanoyloxy $C_{1-8}$ alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a  $C_{6-12}$ aroyloxy $C_{1-8}$ alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the  $Alk^7$  group include  $R^{13a}$  substituents described above.

15

When  $Alk^6$  is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)<sub>2</sub>- or -N( $R^9$ )- groups.

20

Cycloaliphatic or heterocycloaliphatic groups represented by the groups  $R^{13a}$  or  $R^{14}$  include those optionally substituted  $C_{3-10}$ cycloaliphatic or  $C_{3-10}$  heterocycloaliphatic groups described above for  $R^3$ .

25

Aryl or heteroaryl groups represented by the groups  $R^{13a}$  or  $R^{14}$  include mono- or bicyclic optionally substituted  $C_{6-12}$  aromatic or  $C_{1-9}$  heteroaromatic groups as described above for the group  $Ar^1$ . The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

30

When -NHet<sup>1</sup> or -Het<sup>2</sup> forms part of a substituent  $R^{13}$  each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally

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Het<sup>2</sup> may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet<sup>1</sup> or -Het<sup>2</sup> include those R<sup>7</sup> substituents described above.

- 5 Particularly useful atoms or groups represented by R<sup>13</sup> include fluorine, chlorine, bromine or iodine atoms, or C<sub>1-6</sub>alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, e.g. t-butyloxycarbonylpiperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl,
- 10 oxazolidinyl, thiazolidinyl, imidazolidinyl or piperidinyl, C<sub>1-6</sub>hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC<sub>1-6</sub>alkyl, e.g. carboxyethyl, C<sub>1-6</sub>alkylthio e.g. methylthio or ethylthio, carboxyC<sub>1-6</sub>alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, hydroxyC<sub>1-6</sub>alkoxy, e.g. 2-hydroxyethoxy,
- 15 optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C<sub>4-7</sub>cycloalkyl, e.g. cyclobutyl, cyclopentyl, C<sub>5-7</sub>cycloalkoxy, e.g. cyclopentyloxy, haloC<sub>1-6</sub>alkyl, e.g. trifluoromethyl, haloC<sub>1-6</sub>alkoxy, e.g. trifluoromethoxy, C<sub>1-6</sub>alkylamino, e.g. methylamino, ethylamino or propylamino, C<sub>6-12</sub>arylC<sub>1-6</sub>alkylamino, e.g. benzylamino, 4-fluorobenzyl-
- 20 amino or 4-hydroxyphenylethylamino, amino (-NH<sub>2</sub>), aminoC<sub>1-6</sub>alkyl, e.g. aminomethyl or aminoethyl, C<sub>1-6</sub>dialkylamino, e.g. dimethylamino or diethylamino, aminoC<sub>1-6</sub>alkylamino, e.g. aminoethylamino or aminopropyl-
- 25 amino, optionally substituted Het<sup>1</sup>NC<sub>1-6</sub>alkylamino, e.g. 3-morpholino-propylamino, C<sub>1-6</sub>alkylaminoC<sub>1-6</sub>alkyl, e.g. ethylaminoethyl, C<sub>1-6</sub>dialkyl-
- 30 aminoC<sub>1-6</sub>alkyl, e.g. diethylaminoethyl, aminoC<sub>1-6</sub>alkoxy, e.g. aminoethoxy, C<sub>1-6</sub>alkylaminoC<sub>1-6</sub>alkoxy, e.g. methylaminoethoxy, C<sub>1-6</sub>dialkylaminoC<sub>1-6</sub>alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylamino-
- 35 ethoxy, or dimethylaminopropoxy, hydroxyC<sub>1-6</sub>alkylamino, e.g. 2-hydroxy-ethylamino, 3-hydroxypropylamino or 3-hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO<sub>2</sub>H), -CO<sub>2</sub>Alk<sup>7</sup> [where Alk<sup>7</sup> is as defined above], C<sub>1-6</sub>alkanoyl e.g. acetyl, propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC<sub>1-6</sub>alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH<sub>2</sub>, sulphonyl (-SO<sub>3</sub>H), -SO<sub>3</sub>Alk<sup>7</sup>, C<sub>1-6</sub>alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl or propylsulphonyl,

aminosulphonyl ( $-\text{SO}_2\text{NH}_2$ ),  $\text{C}_{1-6}$ alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl  $\text{C}_{1-6}$ dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ( $-\text{CONH}_2$ ),  $\text{C}_{1-6}$ alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl,  $\text{C}_{1-6}$ dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino $\text{C}_{1-6}$ alkylaminocarbonyl, e.g. aminoethylaminocarbonyl,  $\text{C}_{1-6}$ alkylamino $\text{C}_{1-6}$ alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl,  $\text{C}_{1-6}$ dialkylamino $\text{C}_{1-6}$ alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino,  $\text{C}_{1-6}$ alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino,  $\text{C}_{1-6}$ dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino,  $\text{C}_{1-6}$ alkylaminocarbonyl $\text{C}_{1-6}$ alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino,  $\text{C}_{1-6}$ alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino,  $\text{C}_{1-6}$ dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino,  $\text{C}_{1-6}$ alkylaminothiocarbonyl $\text{C}_{1-6}$ alkylamino, e.g. ethylaminothiocarbonylmethylamino,  $-\text{CONHC}(=\text{NH})\text{NH}_2$ ,  $\text{C}_{1-6}$ alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, halo $\text{C}_{1-6}$ alkylsulphonylamino, e.g. trifluoromethylsulphonylamino,  $\text{C}_{1-6}$ dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino ( $-\text{NHSO}_2\text{NH}_2$ ),  $\text{C}_{1-6}$ alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino,  $\text{C}_{1-6}$ dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonyl $\text{C}_{1-6}$ alkylamino, optionally substituted phenylaminosulphonylamino,  $\text{C}_{1-6}$ alkanoylamino, e.g. acetylamino, amino $\text{C}_{1-6}$ alkanoylamino e.g. aminoacetylamino,  $\text{C}_{1-6}$ dialkylamino $\text{C}_{1-6}$ alkanoylamino, e.g. dimethylaminoacetylamino,  $\text{C}_{1-6}$ alkanoylamino $\text{C}_{1-6}$ alkyl, e.g. acetylamino-methyl,  $\text{C}_{1-6}$ alkanoylamino $\text{C}_{1-6}$ alkylamino, e.g. acetamidoethylamino,  $\text{C}_{1-6}$ alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylamino $\text{C}_{1-6}$ alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.



Where desired, two  $R^{13}$  substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a  $C_{1-6}$ alkylenedioxy group such as methylenedioxy or ethylenedioxy.

5

It will be appreciated that where two or more  $R^{13}$  substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by  $R^3$ .

10

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

15

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

20

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

25

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

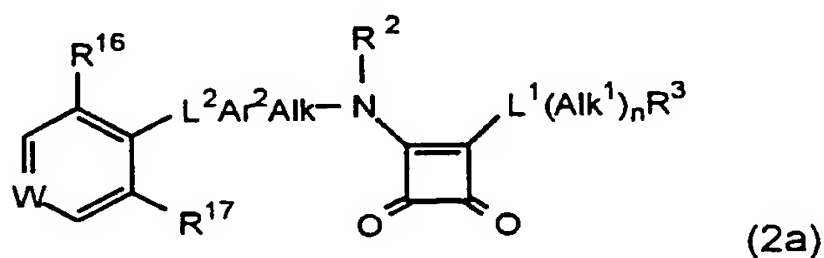
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In the compounds according to the invention the group  $R^1$  is preferably an  $Ar^1L^2Ar^2Alk-$  group. In compounds of this type  $Ar^1$  is preferably an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic

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groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar<sup>1</sup> groups include halogen atoms or optionally substituted alkyl, -OR<sup>5</sup>, -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>6</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -NO<sub>2</sub> or -CN groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar<sup>1</sup> include optionally substituted ten-membered fused-ring heteroaromatic groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups.

A particularly useful group of compounds according to the invention has the formula (2a):



wherein -W= is -CH= or -N=;

R<sup>16</sup> and R<sup>17</sup>, which may be the same or different is each a hydrogen atom or an atom or group -L<sup>3</sup>(Alk<sup>2</sup>)<sub>t</sub>L<sup>4</sup>(R<sup>4</sup>)<sub>u</sub> in which L<sup>3</sup>, Alk<sup>2</sup>, t, L<sup>4</sup>, R<sup>4</sup> and u are as defined previously;

L<sup>1</sup>, L<sup>2</sup>, Ar<sup>2</sup>, Alk, R<sup>2</sup>, Alk<sup>1</sup>, n and R<sup>3</sup> are as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

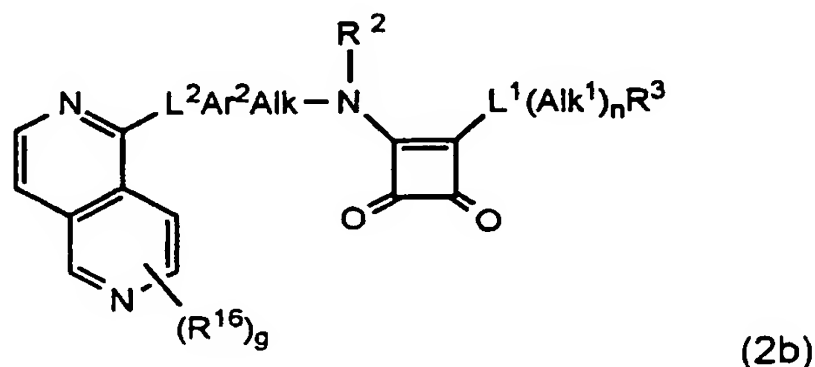
-W= in compounds of formula (2a) is preferably -N=.

R<sup>16</sup> and R<sup>17</sup> in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a

hydrogen atom. Particularly useful  $R^{16}$  and  $R^{17}$  substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially  $-CF_3$ ,  $-CHF_2$  or  $-CH_2F$ , methoxy or halomethoxy, especially  $-OCF_3$ ,  $-OCHF_2$  or  $-OCH_2F$  groups.

5

A further particularly useful group of compounds according to the invention has the formula (2b):



10

wherein  $R^{16}$ ,  $L^1$ ,  $L^2$ ,  $Ar^2$ ,  $Alk$ ,  $R^2$ ,  $Alk^1$ ,  $n$  and  $R^3$  are as defined for formula (2a);

$g$  is zero or the integer 1, 2, 3 or 4;

and the salts, solvates, hydrates and N-oxides thereof.

15

Each  $R^{16}$  atom or group in compounds of formula (2b) may be independently selected from an atom or group  $-L^3(Alk^2)_tL^3(R^4)_u$  in which  $L^3$ ,  $Alk^2$ ,  $t$ ,  $L^4$ ,  $R^4$  and  $u$  are as previously defined. Particularly useful  $R^{16}$  substituents when present in compounds of formula (2b) include halogen atoms, especially fluorine, chlorine or bromine atoms, or methyl, halomethyl, especially  $-CF_3$ , methoxy or halomethoxy, especially  $-OCF_3$ ,  $-CN$ ,  $-CO_2Me$ ,  $-NO_2$ , amino ( $-NH_2$ ), substituted amino ( $-NR^5R^6$ ) and  $-N(R^5)COCH_3$ , especially  $-NHCOCH_3$  groups.

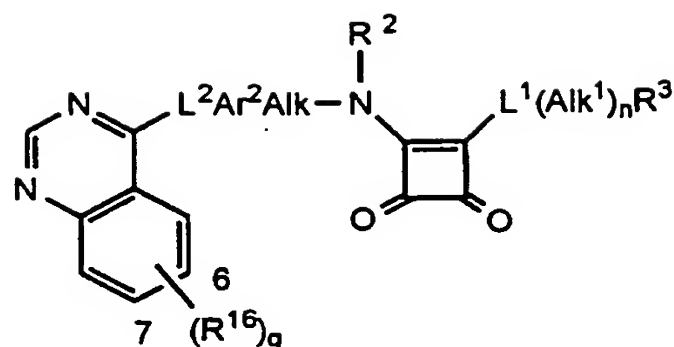
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25 In one preferred group of compounds of formula (2b) each  $R^{16}$  is a hydrogen atom.

Another particularly useful group of compounds according to the invention has the formula (2c):

30

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(2c)

wherein  $R^{16}$ ,  $g$ ,  $L^1$ ,  $L^2$ ,  $Ar^2$ ,  $Alk$ ,  $R^2$ ,  $Alk^1$ ,  $n$  and  $R^3$  are as defined for formula (2b);

5. and the carbon atoms at positions 6 and 7 of the naphthyridine ring are indicated with the appropriate numerals;  
and the salts, solvates, hydrates and N-oxides thereof.

Each  $R^{16}$  atom or group in compounds of formula (2c) may be  
10 independently selected for an atom or group  $-L^3(Alk^2)_tL^4(R^4)_u$  in which  $L^3$ ,  $Alk^2$ ,  $t$ ,  $L^4$ ,  $R^4$  and  $u$  are as previously defined. Particularly useful  $R^{16}$  substituents when present in compounds of formula (2c) include halogen atoms, especially fluorine or chlorine atoms, methyl, halomethyl, especially  
-CF<sub>3</sub>, methoxy or halomethoxy, especially -OCF<sub>3</sub>, -CN, -CO<sub>2</sub>Me, -NO<sub>2</sub>,  
15 amino (-NH<sub>2</sub>), substituted amino (-NR<sup>5</sup>R<sup>6</sup>) and -N(R<sup>5</sup>)COCH<sub>3</sub>, especially -NHCOCH<sub>3</sub> groups.

In one preferred group of compounds of formula (2c)  $g$  is the integer 1 and  $R^{16}$  is a methoxy group, especially a methoxy group present at the 6-  
20 position. In another preferred group of compounds of formula (2c)  $g$  is the integer 2 and each  $R^{16}$  group is a methoxy group, especially a methoxy group present at the 6- and 7-positions.

Alk in compounds of the invention is preferably:

25 -CH- or, especially, -CH<sub>2</sub>CH(R)-.  
|  
CH<sub>2</sub>R

R in the compounds of formulae (1), (2a), (2b) and (2c) is preferably a  
30 -CO<sub>2</sub>H group.

In general in compounds of formulae (1), (2a), (2b) and (2c)  $R^2$  is preferably a hydrogen atom.

- 5 In general in compounds of formula (2a)  $L^2$  is preferably  $L^{2a}$  where  $L^{2a}$  is a  $-\text{CON}(R^8)-$  group, especially  $-\text{CONH}-$ .

10 In general in compounds of formulae (2b) and (2c)  $L^2$  is preferably  $L^{2a}$  where  $L^{2a}$  is an  $-\text{O}-$  atom or  $-\text{N}(R^8)-$  group. An especially useful  $-\text{N}(R^8)-$  group is  $-\text{NH}-$ .

The group  $\text{Ar}^2$  in compounds of formulae (1), (2a), (2b) and (2c) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

15

- In general in compounds of formulae (1), (2a), (2b) and (2c) when  $n$  is zero or the integer 1 the group  $R^3$  may especially be a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted  $\text{C}_{2-6}$ heteroalkyl, particularly  $\text{C}_{1-3}$ alkoxy $\text{C}_{1-3}$ alkyl, especially methoxypropyl, optionally substituted  $\text{C}_{3-7}$ cycloalkyl, especially optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyl or cyclohexyl, optionally substituted  $\text{C}_{5-7}$ heterocycloaliphatic, especially optionally substituted pyrrolidinyl, piperidinyl or thiazolidinyl, especially optionally substituted phenyl and optionally substituted  $\text{C}_{5-7}$ heteroaromatic, especially optionally substituted pyridyl, pyrimidinyl or triazinyl groups. Optional substituents on these groups include in particular  $R^{13}$  atoms or groups where the group is an aromatic or heteroaromatic group and halogen atoms or  $\text{C}_{1-6}$ alkyl, especially methyl, halo $\text{C}_{1-6}$ alkyl, especially trifluoromethyl,  $\text{C}_{1-6}$ alkoxy, especially methoxy, halo $\text{C}_{1-6}$ alkoxy, especially trifluoromethoxy or  $-(L^6)_p(\text{Alk}^5)_qR^{12}$  groups as described earlier where the group is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl, piperidinyl or thiazolidinyl group. Particularly useful  $-(L^6)_p(\text{Alk}^5)_qR^{12}$  groups include those in which  $L^6$  is a  $-\text{CO}-$  group.  $\text{Alk}^5$  in these groups is preferably present (i.e.  $q$  is preferably an integer 1) and in particular is a  $-\text{CH}_2-$  chain.
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- 25
- 30
- 35

Compounds of this type in which  $R^{12}$  is a hydrogen atom or an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, pyridyl or imidazolyl group are particularly preferred.

- 5 In one preferred class of compounds of formulae (1), (2a), (2b) and (2c)  $L^1$  is present as a  $-N(R^8)-$  group. Particularly useful  $-N(R^8)-$  groups include  $-NH-$ ,  $-N(CH_3)-$ ,  $-N(CH_2CH_3)-$  and  $-N(CH_2CH_2CH_3)-$  groups. In this class of compounds  $n$  is preferably the integer 1 and  $Alk^1$  is preferably an optionally substituted straight or branched  $C_{1-6}$ alkylene chain. Particularly  
10 useful  $Alk^1$  chains include  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH(CH_3)CH_2-$  and  $-C(CH_3)_2CH_2-$ .  $R^3$  in this class of compounds is preferably a hydrogen atom.

- In another preferred class of compounds of formulae (1), (2a), (2b) and  
15 (2c)  $L^1$  is a covalent bond,  $n$  is the integer 1 and  $Alk^1$  is an optionally substituted straight or branched  $C_{1-6}$ alkylene chain. Particularly useful  $Alk^1$  chains include optionally substituted  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$  and  $-CH(CH_3)CH_2-$  and especially  $-C(CH_3)_2CH_2-$  chains.  $R^3$  in this class of compounds is preferably a hydrogen atom. A most  
20 especially useful optionally substituted  $Alk^1R^3$  group is  $-C(CH_3)_3$ .

- In another preferred class of compounds of formulae (1), (2a), (2b) and  
(2c),  $L^1$  is a covalent bond,  $n$  is zero and  $R^3$  is an optionally substituted  $C_{5-7}$ heterocycloaliphatic, especially an optionally substituted piperidiny group.  
25 A most especially useful optionally substituted piperidiny group is an optionally substituted piperidin-1-yl group.

Particularly useful compounds of the invention include:

- (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-  
30 dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-t-butyl-3,4-  
dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-[(6,7-Dimethoxy-4-quinazolinyl)amino]phenyl]-2-[(2-N,N-  
diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
35 (S)-3-[4-[(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-  
dioxocyclobut-1-enyl)amino]propanoic acid;

- (S)-3-[4-([6,7-Dimethoxy-4-quinazolinyloxy]phenyl)-2-[(2-*N,N*-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-([6,7-Methoxy-4-quinazolinyloxy]phenyl)-2-[(2-*N,N*-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
5 (S)-3-[4-([2,6-Naphthyridin-1-yl]amino)phenyl]-2-[(2-*N,N*-dipropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-([2,6-Naphthyridin-1-yl]oxy)phenyl]-2-[(2-*N,N*-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-([2,6-Naphthyridin-1-yl]amino)phenyl]-2-[(2-piperidin-1-yl-3,4-  
10 dioxocyclobut-1-enyl)amino]propanoic acid;  
(*R*)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[(2-*N,N*-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
(S)-3-[4-([2,6-Naphthyridin-1-yl]oxy)phenyl]-2-[(2-*N,N*-dipropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
15 (S)-3-[4-([2,6-Naphthyridin-1-yl]amino)phenyl]-2-[(2-*N*, -ethyl-*N*-isopropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;  
and the salts, solvates, hydrates and N-oxides thereof.

20 The compounds according to the invention are generally of use in modulating cell adhesion. Thus for example when R<sup>1</sup> in compounds of the invention is an  $\alpha_4$ -integrin binding groups the compounds are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role.

25 Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

30 In another example when R<sup>1</sup> is an  $\alpha_v$ -integrin binding group the compounds may be of use in the prophylaxis and treatment of diseases or disorders involving inappropriate growth or migration of cells. Particular diseases include inflammatory diseases, and diseases involving angiogenesis, bone resorption or cellular or matrix over-expression.



- Particular uses to which these compounds of the invention may be put include the treatment or inhibition of tumour growth and metastasis; retinopathy; macular degeneration psoriasis; rheumatoid arthritis; osteoporosis; bone resorption following or due to joint replacement, hypercalcemia or malignancy, Paget's disease, glucocorticoid treatment, immunisation-induced osteopenia, hyperparathyroidism or periodontal disease, vascular restenosis, atherosclerosis; inflammatory bowel disease; and psoriasis.
- 10 For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.
- 15 Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.
- 20 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.
- 35

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

5 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

10 The compounds of formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of formula (1) may be coated on particles such as microscopic gold particles.

20 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

25 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

30 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

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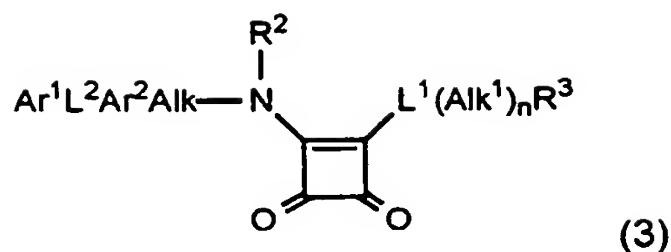
The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg  
5 e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

10

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols  $Ar^1$ ,  $Ar^2$ , Alk,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $L^1$ ,  $L^2$ ,  $Alk^1$  and  $n$  when used in the formulae  
15 depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the  
20 reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of  
25 protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

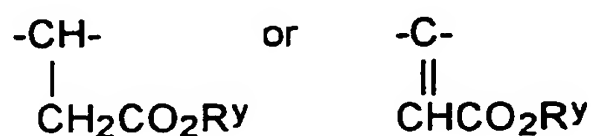
30 Thus according to a further aspect of the invention, a compound of formula (1) in which R is a  $-CO_2H$  group may be obtained by hydrolysis of an ester of formula (3):

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where  $\text{Alk}$  represents a group

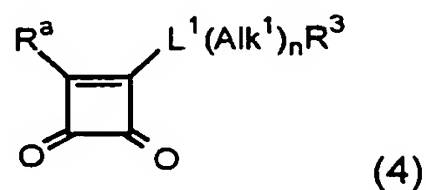
5  $-\text{CH}_2\text{CH}(\text{CO}_2\text{R}^y)-$ ,  $-\text{CH}=\text{CH}(\text{CO}_2\text{R}^y)-$ ,



[where R<sup>y</sup> is an alkyl group for example a C<sub>1-6</sub>alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of RY, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

According to a further aspect of the invention a compound of formula (1) may be prepared by displacement of a leaving group from a compound of formula (4):



where R<sup>a</sup> is a leaving group, with an amine R<sup>1</sup>R<sup>2</sup>NH or a salt thereof. Suitable leaving groups represented by R<sup>a</sup> include halogen atoms, especially chlorine and bromine atoms, or alkoxy, e.g. methoxy, ethoxy or

isopropoxy, aryloxy, e.g. dinitrophenyloxy, or aralkoxy, e.g. benzyloxy, groups.

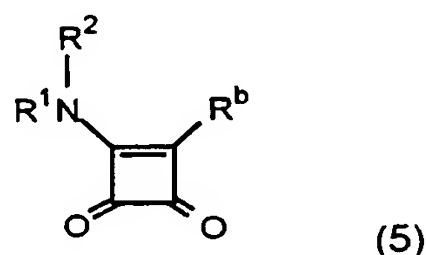
The reaction may be performed in an inert solvent or mixture of solvents, for example a substituted amide such as dimethylformamide, an alcohol such as ethanol and/or a halogenated hydrocarbon such as dichloromethane, at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine  $R^1R^2NH$  is used, an organic base such as diisopropylethylamine can be added.

10

Any carboxylic acid group present in the intermediate of formula (4) or the amine  $R^1R^2NH$  may need to be protected during the displacement reaction, for example as an ethyl ester. The desired acid may then be obtained through subsequent hydrolysis, for example as particularly described above and generally described below.

15

It will be appreciated that the displacement reaction may also be performed on a compound of formula (5):



20

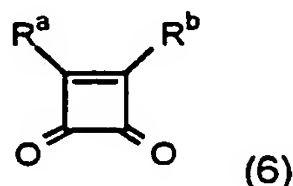
where  $R^b$  is a leaving group as defined for  $R^a$  using an intermediate  $R^3(Alk^1)_nL^1H$  where  $-L^1H$  is a functional group such as an amine ( $-NH_2$ ) using the reaction conditions just described.

25

Where desired the displacement reaction may also be performed on an intermediate of formulae (4) or (5),  $R^1R^2NH$  or  $R^3(Alk^1)_nL^1H$  which is linked, for example via its  $R^1$  or  $R^3$  group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen.

30

Intermediates of formulae (4) and (5) are either readily available or may be prepared from an intermediate of formula (6):



- 5 where  $R^a$  and  $R^b$  are as previously defined and an amine  $R^1R^2NH$  or intermediate  $R^3(Alk^1)_nL^1H$  by displacement as just described for the preparation of compounds of formula (1).
- 10 Intermediates of formulae  $R^1R^2NH$  and  $R^3(Alk^1)_nL^1H$  may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional
- 15 alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds.
- 20 Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a  $-L^1H$  or  $-L^2H$  group (where  $L^1$  and  $L^2$  is each a linker atom or group) may be treated with a coupling agent  $R^3(Alk^1)_nX^1$  or  $Ar^1X^1$  respectively in which  $X^1$  is a leaving atom or group such as a
- 25 halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluene-sulphonyloxy group.
- 30 The reaction may be carried out in the presence of a base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine,

such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

- 5 Intermediates of formula  $\text{Ar}^1\text{X}^1$  and  $\text{R}^3(\text{Alk}^1)_n\text{X}^1$  are generally known, readily available compounds or may be prepared from known compounds by standard substitution and other synthetic procedures, for example as described herein. Thus for example compounds of formula  $\text{Ar}^1\text{X}^1$  in which, for example,  $\text{Ar}^1$  represents a 2,6-naphthyridine group may be  
10 prepared from alcohols of formula  $\text{Ar}^1\text{OH}$  by reaction with a halogenating agent, for example a phosphorous oxyhalide such as phosphorous oxychloride at an elevated temperature e.g. 110°C.

- Intermediate alcohols of formula  $\text{Ar}^1\text{OH}$  in which, for example,  $\text{Ar}^1$   
15 represents a 2,6-naphthyridine group may be prepared by methods well known to a person skilled in the art, e.g. by the method of Sakamoto, T. *et al* [Chem. Pharm. Bull. 33, 626-633, (1985)].

- Alternatively alkylating agents of formula  $\text{Ar}^1\text{X}^1$  in which, for example,  $\text{Ar}^1$   
20 represents a 2,6-naphthyridine group may be prepared by reaction of a 2,6-naphthyridine N-oxide or N, N'-dioxide with a halogenating agent, e.g. a phosphorous oxyhalide such as phosphorous oxychloride to give a 1-halo or 1,5-dihalo-2,6-naphthyridine respectively. In the case of 1,5-dihalo-2,6-naphthyridines each halogen atom may be substituted separately by a  
25 reagent such as  $\text{HL}^2\text{Ar}^2\text{AlkN}(\text{R}^2)\text{H}$  or  $\text{HL}^3(\text{Alk}^2)_t\text{L}^4(\text{R}^4)_u$  by the particular methods just described above.

- 2,6-Naphthyridine N-oxides and N,N'-dioxides may be generated from the corresponding 2,6-naphthyridines group by the general methods of  
30 synthesis of N-oxides described below or they may be synthesised by the methods of Numata, A. *et al* (Synthesis, 1999, 306-311).

- Further alkylating agents of formula  $\text{Ar}^1\text{X}^1$  in which, for example,  $\text{Ar}^1$  represents a 2,6-naphthyridine, may be prepared by the methods of  
35 Giacomello G. *et al* (Tetrahedron Letters 1965, 1117-1121), Tan, R. and Taurins, A. (Tetrahedron Letters 1965, 2737-2744), Ames, D. E. and



Dodds, W. D. (J. Chem. Soc. Perkin 1 1972, 705-710) and Alhaique, F. *et al* (Tetrahedron Letters, 1975, 173-174).

5 In a further example intermediates of formula  $R^1R^2NH$  may be obtained by reaction of a compound of formula  $Ar^1L^2H$  with a compound of formula  $X^1Ar^2AlkN(R^2)H$  under the reaction conditions just described

10 Compounds of formula  $Ar^1L^2H$  in which, for example  $Ar^1$  represents a 2,6-naphthyridine and  $L^2$  is a  $-N(R^8)-$  group, may be prepared from substituted 4-cyano-3-cyanomethylpyridines by the methods of Alhaique, F. *et al* (*ibid* and Gazz. Chim. Ital. 1975, 105; 1001-1009) or from 3-formylpyridines by the methods of Molina, P. *et al* (Tetrahedron 1992, 48, 4601-4616).

15 In another example, compounds containing a  $-L^1H$  or  $-L^2H$  or group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which  $X^1$  is replaced by a  $-C(O)X^2$ ,  $C(S)X^2$ ,  $-N(R^8)COX^2$  or  $-N(R^8)C(S)X^2$  group in which  $X^2$  is a leaving atom or group as described for  $X^1$ . The reaction may be performed in the presence of a base, such as a hydride,  
20 e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for  
25 example one of the alkylating agents described above in which  $X^1$  is replaced by a  $-CO_2H$  group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as  
30 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

35 In a further example compounds may be obtained by sulphonylation of a compound containing an  $-OH$  group by reaction with one of the above alkylating agents but in which  $X^1$  is replaced by a  $-S(O)Hal$  or  $-SO_2Hal$

group in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

5

In another example, compounds containing a  $-L^1H$  or  $-L^2H$  group as defined above may be coupled with one of the alkylation agents just described but in which  $X^1$  is replaced by an  $-OH$  group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

10

In a further example, ester groups  $-CO_2R^5$ ,  $-CO_2Alk^3$  or  $-CO_2Alk^7$  in the compounds may be converted to the corresponding acid  $[-CO_2H]$  by acid- or base-catalysed hydrolysis depending on the nature of the groups  $R^5$ ,  $Alk^3$  or  $Alk^7$ . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

15

20

In a further example,  $-OR^5$  or  $-OR^{14}$  groups [where  $R^5$  or  $R^{14}$  each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol  $-OH$  by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around  $-78^\circ C$ .

25

Alcohol  $[-OH]$  groups may also be obtained by hydrogenation of a corresponding  $-OCH_2R^{14}$  group (where  $R^{14}$  is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example,  $-OH$  groups may be generated from the corresponding ester  $[CO_2Alk^5$  or  $CO_2R^5]$  or aldehyde  $[-CHO]$  by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

30

35

In another example, alcohol -OH groups in the compounds may be converted to a corresponding -OR<sup>5</sup> or -OR<sup>14</sup> group by coupling with a reagent R<sup>5</sup>OH or R<sup>14</sup>OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as  
5 diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO<sub>2</sub>NHR<sup>3</sup> or -NHSO<sub>2</sub>NHAr<sup>1</sup>] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH<sub>2</sub>] with a sulphamide R<sup>3</sup>NHSO<sub>2</sub>NH<sub>2</sub> or  
10 Ar<sup>1</sup>NHSO<sub>2</sub>NH<sub>2</sub> in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a -NHCSAr<sup>1</sup>, -CSNHAr<sup>1</sup>, -NHCSR<sup>3</sup> or -CSNHR<sup>3</sup> may be prepared by treating a corresponding  
15 compound containing a -NHCOAr<sup>a</sup>, -CONHAr<sup>1</sup>, -NHCOR<sup>3</sup> or -CONHR<sup>3</sup> group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

20 In a further example amine (-NH<sub>2</sub>) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxymethylborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in  
25 the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH<sub>2</sub>] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with  
30 hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO<sub>2</sub>] group may be reduced to an amine [-NH<sub>2</sub>], for example by catalytic hydrogenation using for example hydrogen  
35 in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an

alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

5 Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile;  
10 a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L<sup>1</sup> or L<sup>2</sup> may be oxidised to the corresponding  
15 sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

In another example compounds of formula Ar<sup>1</sup>X<sup>1</sup> (where X<sup>1</sup> is a halogen atom such as a chlorine, bromine or iodine atom) may be converted to  
20 such compounds as Ar<sup>1</sup>CO<sub>2</sub>R<sup>20</sup> (in which R<sup>20</sup> is an optionally substituted alkyl, aryl or heteroaryl group), Ar<sup>1</sup>CHO, Ar<sup>1</sup>CHCHR<sup>20</sup>, Ar<sup>1</sup>CCR<sup>20</sup>, Ar<sup>1</sup>N(R<sup>20</sup>)H, Ar<sup>1</sup>N(R<sup>20</sup>)<sub>2</sub>, for use in the synthesis of for example compounds of formula R<sup>1</sup>R<sup>2</sup>NH, using such well known and commonly  
25 used palladium mediated reaction conditions as are to be found in the general reference texts Encyclopedia of Reagents for Organic Synthesis, Editor-in Chief Paquette, L. A., John Wiley and Sons, 1995 and Comprehensive Organic Functional Group Transformations, Editors-in-Chief Katritzky, A. R. *et al*, Pergamon, 1995.

30 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively  
35 by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

30	NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
	MeOH - methanol;	BOC - butoxycarbonyl;
	DCM - dichloromethane;	AcOH - acetic acid;
	DIPEA - diisopropylethylamine;	EtOH - ethanol;
	Pyr - pyridine;	Ar - aryl;
35	DMSO - dimethylsulphoxide;	iPr - isopropyl;
	Et <sub>2</sub> O - diethylether;	Me - methyl;

- THF - tetrahydrofuran, DMF - N,N-dimethylformamide;  
Fmoc - 9-fluorenylmethoxycarbonyl; br - broad;  
obs - obscured; app - apparent;  
dil - dilute; RT - room temperature;  
5 Bu - butyl; DIPEA - diisopropylethylamine

All NMR's were obtained at 300MHz.

10 **INTERMEDIATE 1**

**3,5-Dichloropyridine-4-carboxylic acid**

- A solution of 3,5-dichloropyridine (5.00g, 33.8mmol) in THF (25ml) was added to a solution of LDA [generated from nBuLi (2.5M solution in hexanes, 14.9ml, 37.2mmol) and diisopropylamine (4.10g, 5.7ml, 40.6mmol)] in THF (25ml) at -78° under nitrogen, to give a yellow/brown slurry. The reaction was stirred for 30min at -78° then CO<sub>2</sub> gas was bubbled through to give a clear brown solution that slowly gave a precipitate, warmed to RT over 2h, then quenched with water (20ml) and partitioned between Et<sub>2</sub>O (100ml) and 1M NaOH (100ml). The aqueous layer was separated and acidified to pH1 with concentrated hydrochloric acid and then extracted with 10% MeOH in DCM (100ml x 3). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent removed under vacuum to give a brown solid that was recrystallised from ethanol and dried under vacuum to give the title compound as pinkish crystals (2.63g, 41%). δH (DMSO-d<sub>6</sub>) 8.74 (2H, s). δC (DMSO-d<sub>6</sub>) 163.5, 147.7, 141.0, 126.7
- 15  
20  
25

**INTERMEDIATE 2**

- Ethyl (S)-3-(4-[3,5-dichloropyrid-4-ylcarboxamido]phenyl)-2-(t-butoxycarbonyl amino)propionate**
- 30

- A slurry of the compound of Intermediate 1 (51.2g, 0.267mol) in DCM (195ml) and thionyl chloride (195ml, 2.67mol) was treated with DMF (5 drops) and heated to reflux for 4h. The reaction was concentrated *in vacuo* and azeotroped with toluene (2 x 50ml) to give a yellow solid which was used without further purification. A solution of ethyl-(S)-3-(4-aminophenyl)-2-(t-butoxycarbonyl amino)propionate (130.8g, 0.425mol) in
- 35

DCM (800ml) was cooled to 0° and treated with NMM (56.0ml, 0.51mol), stirred 5 minutes and then a solution of the acid chloride (98.3g, 0.468mol) in DCM (200ml) was added dropwise keeping the reaction temperature below 5°. The reaction was stirred for 1h, quenched with NaHCO<sub>3</sub> solution (500ml), the organic layer separated, washed with NaHCO<sub>3</sub> solution (500ml), 10% citric acid solution (500ml) and NaHCO<sub>3</sub> solution (500ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a yellow solid which was recrystallised (EtOAc/hexane) to give the title compound, 140g, 69%.  $\delta$ H (DMSO d<sub>6</sub>), 8.8 (2H, s), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 4.0 (3H, m), 3.4 (2H, b s), 2.9 (1H, m), 2.8 (1H, m), 1.3 (9H, s), 1.25 (3H, t). m/z (ES<sup>+</sup>, 70V) 504 (MNa<sup>+</sup>).

### INTERMEDIATE 3

#### Ethyl (S)-3-[4-(3,5-dichloropyrid-4-yl carboxamido)phenyl]-2-amino propionate hydrochloride

A solution of the compound of Intermediate 2 (70g, 0.146mol) in EtOAc (500ml) and 1,4-dioxan (50ml) was treated with a solution of HCl in EtOAc (500ml, 3M), and stirred at RT for 4h. The reaction was concentrated *in vacuo* to give a yellow solid which was triturated with Et<sub>2</sub>O then recrystallised (EtOAc/hexane) to give the title compound (59.3g, 92%).  $\delta$ H (DMSO d<sub>6</sub>), 11.10 (1H, s), 8.70 (2H, s), 7.55 (2H, d,  $\downarrow$  8.4Hz), 7.25 (2H, d,  $\downarrow$  8.4Hz), 4.10 (3H, m), 3.10 (2H, m), 1.10 (3H, m). m/z (ES<sup>+</sup>, 70V) 382 (MH<sup>+</sup>).

### INTERMEDIATE 4

#### 3-(tert-Butyl)-4-isopropoxy-3-cyclobutene-1,2-dione

tert-Butyl lithium (2.29ml of a 1.7M solution in pentane, 3.9mmol) was added to a solution of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (594mg, 3mmol) in THF (30ml) at -78°C. After 5h trifluoroacetic anhydride (636 $\mu$ l, 4.5mmol) was added and stirring continued at -78°C for 30min. The cold mixture was poured into NH<sub>4</sub>Cl(aq), extracted with EtOAc, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. Column chromatography (SiO<sub>2</sub>; EtOAc/hexane, 15:85) gave the title compound as a mobile yellow oil (408mg, 69%).  $\delta$ H (CDCl<sub>3</sub>) 5.43 (1H, sept,  $\downarrow$  6.2Hz), 1.45 (6H, d,  $\downarrow$  6.2Hz) and 1.33 (9H, s); m/z (ES<sup>+</sup>, 70V) 197 (M<sup>+</sup> + H).

**INTERMEDIATE 5****1-Chloro-2,6-naphthyridine**

1-Hydroxy-2,6-naphthyridine (550mg) [prepared according to the method of Sakamoto, T. *et al* Chem. Pharm. Bull. 33, 626, (1985)] was stirred with  
5 phosphorous oxychloride (10ml) at 110° for 5h. The volatiles were removed *in vacuo* and the residue treated carefully with ice. After diluting with water (to ~25ml), solid NaHCO<sub>3</sub> was added to neutralise and the product extracted into EtOAc (2 x 80ml). The combined organic extracts were dried (MgSO<sub>4</sub>), evaporated *in vacuo*, and the crude product  
10 chromatographed (SiO<sub>2</sub>; EtOAc) affording the title compound as a slightly yellow solid (420mg, 68%).  $\delta$ H (CDCl<sub>3</sub>) 9.35 (1H, s), 8.82 (1H, d,  $\downarrow$  5.9Hz), 8.48 (1H, d,  $\downarrow$  5.6Hz), 8.00 (1H, d,  $\downarrow$  5.9Hz), 7.74 (1H, d,  $\downarrow$  5.6Hz);  $m/z$  (ES<sup>+</sup>, 70V) 165 and 167 (MH<sup>+</sup>).

**INTERMEDIATE 6****Ethyl (S)-3-{4-[(2,6-naphthyridin-1-yl)amino]phenyl}-2-[N-(t-butyloxy carbonyl) amino]propanoate**

Ethyl (S)-3-(4-aminophenyl)-2-[N-(t-butyloxycarbonyl)amino]propanoate (600mg, 1.95mmol), Intermediate 5 (350mg, 2.13mmol) and DIPEA  
20 (276mg, 372 $\mu$ l, 2.13mmol) in 2-ethoxyethanol (0.5ml) were stirred at 130° under N<sub>2</sub> for several hours. The reaction was partitioned between EtOAc (70ml) and saturated aqueous NaHCO<sub>3</sub> (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were washed with brine (10ml), dried (MgSO<sub>4</sub>)  
25 and evaporated *in vacuo* to afford a dark oil. Chromatography (SiO<sub>2</sub>; 3% MeOH/DCM) gave the title compound as a dull orange foam (360mg, 42%).  $\delta$ H (CDCl<sub>3</sub>) 9.19 (1H, s), 8.67 (1H, d,  $\downarrow$  5.9Hz), 8.24 (1H, d,  $\downarrow$  5.8Hz), 7.66 (1H, d,  $\downarrow$  5.9Hz), 7.65 (2H, d,  $\downarrow$  8.5Hz), 7.21 (1H, d,  $\downarrow$  5.8Hz), 7.16 (2H, d,  $\downarrow$  8.5Hz), 7.15 (1H, obscured s), 5.05-4.97 (1H, m), 4.60-4.51  
30 (1H, m), 4.19 (2H, q,  $\downarrow$  7.1Hz), 3.17-3.04 (2H, m), 1.44 (9H, s), 1.27 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 459 (MNa<sup>+</sup>), 437 (MH<sup>+</sup>).

**INTERMEDIATE 7****Ethyl (S)-2-amino-3-{4-[(2,6-naphthyridin-1-yl)amino]phenyl} propanoate**

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Intermediate 6 (360mg) was treated with a solution of trifluoroacetic acid (10ml) and DCM (10ml) and stirred at RT for 2h. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (80ml) and saturated aqueous NaHCO<sub>3</sub> (30ml). The phases were separated and the aqueous layer re-extracted with EtOAc (3 x 30ml). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford the title compound as a dark orange viscous oil (280mg, 100%).  $\delta$ H (CDCl<sub>3</sub>) 9.18 (1H, s), 8.66 (1H, d,  $\downarrow$  5.9Hz), 8.22 (1H, d,  $\downarrow$  5.8Hz), 7.67 (1H, d,  $\downarrow$  5.9Hz), 7.64 (2H, d,  $\downarrow$  8.5Hz), 7.22 (2H, d,  $\downarrow$  8.5Hz), 7.19 (1H, d,  $\downarrow$  5.8Hz), 4.20 (2H, q,  $\downarrow$  7.1Hz), 3.73 (1H, dd, J 7.9, 5.1Hz), 3.10 (1H, dd,  $\downarrow$  13.6, 5.2Hz), 2.87 (1H, dd,  $\downarrow$  13.6, 7.9Hz), 1.70 (3H, br s), 1.28 (3H, t, 7.1Hz); m/z (ES<sup>+</sup>, 70V) 337 (MH<sup>+</sup>).

#### INTERMEDIATE 8

##### 15 Methyl (S)-2-(*t*-butyloxycarbonylamino)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]propanoate

To *N*-(*t*-butyloxycarbonyl) tyrosine methyl ester (1.42g, 4.82mmol) in dry DMF (10ml) was added 1-chloro-2,6 naphthyridine (0.79g, 4.82mmol) and cesium carbonate (1.65g, 5.06 mmol) and the reaction stirred at 45° under N<sub>2</sub> for 2 days. The DMF was evaporated, EtOAc added and washed (3x) with water, dried (MgSO<sub>4</sub>), and evaporated *in vacuo*. The residue was chromatographed (SiO<sub>2</sub>; 40 to 100% EtOAc/isohexane) to afford the title compound as white foam (1.61g, 82%).  $\delta$ H (CDCl<sub>3</sub>) 9.29 (1H, s), 8.76 (1H, d,  $\downarrow$  5.74Hz), 8.17 (1H, d,  $\downarrow$  5.74Hz), 8.11 (1H, d,  $\downarrow$  5.8Hz), 7.43 (1H, d,  $\downarrow$  5.8Hz), 7.22-7.18 (3H, m), 5.03 (1H, br s), 4.61 (1H, br s), 3.75 (3H, s), 3.15-3.05 (2H, m), 1.44 (9H, s); m/z (ES<sup>+</sup>, 70V) MH<sup>+</sup> 424.

#### INTERMEDIATE 9

##### 30 Ethyl (S)-2-(*N*-*t*-butyloxycarbonylamino)-3-[4-(isoquinolin-1-ylamino)phenyl]propanoate

A stirred solution of ethyl (S)-3-(4-aminophenyl)-2-(*N*-*t*-butyloxycarbonylamino)propanoate (3.08g, 10.0mmol), 1-chloroisoquinoline (1.80g, 11.0mmol) and *N,N*-diisopropylethylamine (1.42g, 1.91ml, 11.0mmol) in 2-ethoxyethanol (1.0ml) was heated at 130° for 4h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc (120ml) and saturated aqueous NaHCO<sub>3</sub> (50ml). The phases were separated and the

aqueous layer was re-extracted with EtOAc (80ml). The combined organic extracts were washed with brine (30ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The obtained dark oil was chromatographed (silica; 20-30% EtOAc/hexane) to afford the title compound as a pink oil which crystallised on standing (2.78g, 64%).  $\delta$ H (CDCl<sub>3</sub>) 8.07 (1H, d,  $\downarrow$  5.8Hz), 7.93 (1H, d,  $\downarrow$  8.4Hz), 7.72 (1H, d,  $\downarrow$  7.5Hz), 7.63 (1H, d), 7.61 (2H, d,  $\downarrow$  8.5Hz), 7.51 (1H, t,  $\downarrow$  6.8Hz), 7.23 (1H, br s), 7.10 (1H, br s), 7.10 (2H, d,  $\downarrow$  6.8Hz), 5.02 (1H, br d,  $\downarrow$  8.0Hz), 4.54 (1H, br m), 4.16 (2H, t,  $\downarrow$  7.1Hz), 3.05 (2H, br m), 1.43 (9H, s), 1.25 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 60V) 436 (MH<sup>+</sup>).

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### INTERMEDIATE 10

#### (S)-Ethyl 2-amino-3-[4-(isoquinolin-1-ylamino)phenyl]propanoate

A stirred solution of Intermediate 9 (2.70g) in EtOAc (100ml) was treated with HCl gas until turbidity and precipitation was seen to occur. The reaction mixture was stirred at ambient temperature for an additional 0.5h. The reaction was purged with nitrogen then diluted with EtOAc (50ml) and saturated aqueous NaHCO<sub>3</sub> (50ml). Sufficient solid NaHCO<sub>3</sub> was added to ensure full neutrality. The phases were separated and the aqueous layer re-extracted with EtOAc (2 x 40ml). The combined organic extracts were washed with brine (20ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to afford the title compound as a light orange oil (2.10g, q).  $\delta$ H (CDCl<sub>3</sub>) 8.06 (1H, d,  $\downarrow$  5.8Hz), 7.91 (1H, d,  $\downarrow$  8.3Hz), 7.71 (1H, d,  $\downarrow$  7.9Hz), 7.63 (1H, obs. signal), 7.59 (2H, d,  $\downarrow$  8.4Hz), 7.49 (1H, app.t,  $\downarrow$  7.8Hz), 7.25 (1H, br s), 7.15 (1H, d,  $\downarrow$  8.4Hz), 7.09 (1H, d,  $\downarrow$  5.8Hz), 4.17 (2H, q,  $\downarrow$  7.2Hz), 3.68 (1H, dd,  $\downarrow$  7.7, 5.1Hz), 3.06 (1H, dd,  $\downarrow$  14.6, 5.1Hz), 2.81 (1H, dd,  $\downarrow$  13.6, 7.9Hz), 1.58 (2H, br s), 1.26 (3H, t,  $\downarrow$  7.0Hz);  $m/z$  (ES<sup>+</sup>, 60V) 435.9 (MH<sup>+</sup>).

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### INTERMEDIATE 11

#### Ethyl (E)-3-[4-[(tert-Butoxycarbonyl)amino]phenyl]-2-propenoate

Ethyl 4-aminocinnamate (2.5g, 13.1mmol) was dissolved in THF (25ml) and treated with di-tert-butyl dicarbonate (3.14g). The solution was refluxed for 16h and then allowed to cool. The product was extracted into EtOAc and washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed. The crude product was purified by column chromatography (SiO<sub>2</sub>; EtOAc/hexane 1:9) to give the title compound

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(2.82g, 74%) as a white solid.  $\delta$ H (CDCl<sub>3</sub>) 7.62 (1H, d,  $\downarrow$  16.0Hz), 7.45 (2H, d,  $\downarrow$  8.8Hz), 7.38 (2H, d,  $\downarrow$  8.8Hz), 6.63 (1H, br s), 6.33 (1H, d,  $\downarrow$  16.0Hz), 4.12 (2H, q,  $\downarrow$  7.1Hz), 1.52 (9H, s), 1.25 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 314 (MNa<sup>+</sup>).

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### INTERMEDIATE 12

#### Ethyl (3S)-3-{4-[(tert-Butoxycarbonyl)amino]phenyl}-3-{N-benzyl[(1R)-1-phenylethyl] amino}propanoate

Intermediate 11 (1.0g, 3.44mmol) was dissolved in THF (25ml), treated with sodium hydride and left to stir for 20 mins. (R)-(+)-N-Benzyl-(methylbenzylamine (1.44ml) in THF (25ml) at 0° was treated with n-butyllithium (2.75ml, 2.5M in hexanes) and the purple solution left to stir for 20 mins then cooled to -78° and the ester anion added slowly. The reaction mixture was stirred at -78C for 4h then quenched with ammonium chloride solution, extracted into EtOAc, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed. The crude product was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (1.14g, 66%) as a white solid.  $\delta$ H (CDCl<sub>3</sub>) 7.42-7.17 (14H, m), 6.45 (1H, br s), 4.39 (1H, dd,  $\downarrow$  9.4, 5.5Hz), 3.99 (1H, q, J 6.9Hz), 3.93 (2H, qd,  $\downarrow$  7.1, 2.4Hz), 3.72 (1H, d,  $\downarrow$  14.7Hz), 3.64 (1H, d,  $\downarrow$  14.7Hz), 2.63 (1H, dd,  $\downarrow$  14.7, 5.5Hz), 2.52 (1H, dd,  $\downarrow$  14.7, 9.5Hz), 1.52 (9H, s), 1.22 (3H, d,  $\downarrow$  6.9Hz), 1.06 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 503 (MH<sup>+</sup>).

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### INTERMEDIATE 13

#### Ethyl (3S)-3-amino-3-{4-[(tert-Butoxycarbonyl)amino]}phenyl-propanoate

Intermediate 12 (312mg, 0.62mmol) in MeOH (5ml) was treated with formic acid (0.1ml) and 10% palladium on carbon. The reaction mixture was heated to reflux for 30 mins then cooled, filtered through celite™ and the solvent removed to give the title compound (195mg, 100%) as an oil.  $\delta$ H (CDCl<sub>3</sub>) 8.05 (2H, br s), 7.28 (2H, d, J 8.5Hz), 7.21 (2H, d,  $\downarrow$  8.5Hz), 6.92 (1H, br s), 4.48 (1H, dd,  $\downarrow$  8.4, 5.7Hz), 4.05 (2H, q,  $\downarrow$  7.1Hz), 3.6 (1H, dd,  $\downarrow$  17.2, 8.4Hz), 2.79 (1H, dd,  $\downarrow$  17.2, 5.7Hz), 1.44 (9H, s), 1.14 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 331 (MNa<sup>+</sup>).

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### INTERMEDIATE 14

**Methyl (R)-3-[(tert-Butoxycarbonyl)amino]-3-(4-hydroxyphenyl)-propanoate**

Methyl (3R)-(3-amino)-3-(4-hydroxyphenyl)propanoate [S. G. Davies and O. Ichihara, Tetrahedron Asymmetry, (1991), 2, 183-186] (346mg, 1.78mmol) was dissolved in dioxan (5ml) and sodium bicarbonate solution (5ml) added. The solution was treated with di-tert-butyl dicarbonate (407mg, 1.86mmol) and stirred vigorously for 16h. The solution was diluted with water, and the product extracted into EtOAc (x2), washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed. The product was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to give the title compound (211mg, 42%) as a white solid.  $\delta$ H (CDCl<sub>3</sub>) 7.06 (2H, d,  $\downarrow$  8.6Hz), 6.66 (2H, d,  $\downarrow$  8.6Hz), 5.48 (1H, br), 4.98 (2H, br m), 3.61 (3H, s), 2.78 (2H, m), 1.42 (9H, s). m/z (ES<sup>+</sup>, 70V) 318 (MNa<sup>+</sup>).

**INTERMEDIATE 15**

**Methyl (3R)-3-[(tert-Butoxycarbonyl)amino]-3-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]propanoate**

Intermediate 14 (420mg, 1.42mmol) in DMF (4ml) was treated with potassium carbonate (394mg) and 4-chloro-6,7-dimethoxyquinazoline (320mg). The solution was stirred for 48h and then water (20ml) was added. The mixture was extracted with EtOAc (x 2), washed with water (x 3), brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed to give the title compound (657mg, 96%) as a foamy yellow solid.  $\delta$ H (DMSO d<sub>6</sub>) 8.53 (1H, s), 7.53 (1H, s), 7.40 (2H, d,  $\downarrow$  8.6Hz), 7.37 (1H, s), 7.24 (2H, d,  $\downarrow$  8.6Hz), 4.96 (1H, m, CH), 3.98 (3H, s), 3.95 (3H, s), 3.57 (3H, s), 2.77 (2H, m), 1.36 (9H, s). m/z (ES<sup>+</sup>, 70V) 484 (MH<sup>+</sup>).

**INTERMEDIATE 16**

**Methyl (3R)-3-Amino-3-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]propanoate**

Intermediate 15 (650mg, 1.35mmol) was dissolved in EtOAc (10ml) and HCl gas was bubbled through. The reaction mixture was stirred for 2h and the solvent removed to give the title compound (589mg, 100%) as an oil.  $\delta$ H (DMSO d<sub>6</sub>) 8.66 (1H, s), 7.65 (2H, d,  $\downarrow$  8.7Hz), 7.58 (1H, s), 7.44 (1H, s), 7.39 (2H, d,  $\downarrow$  8.7Hz), 3.99 (3H, s), 3.97 (3H, s), 3.58 (3H, s), 3.22 (1H,

dd,  $\downarrow$  16.3, 6.1Hz), 3.05 (1H, dd,  $\downarrow$  16.3, 8.5Hz). m/z (ES<sup>+</sup>, 70V) 384 (MH<sup>+</sup>).

#### INTERMEDIATE 17

5 Methyl (S)-3-[4-[(3-phenyl-1-quinazolinyl)amino]phenyl]-[2-(tert-butoxycarbonyl)amino]propanoate

Methyl (2S)-[2-(tert-butoxycarbonyl)amino]-3-(4-aminophenyl)propanoate (500mg, 1.7mmol) and 4-chloro-2-phenylquinazoline (408mg) were dissolved in 2-ethoxyethanol (5ml) with Hunigs base (0.6ml) and the  
10 solution heated at 120°C for 16h. The solution was cooled and concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 25:1) to give the title compound (682mg, 81%) as a brown foamy solid.  $\delta$ H (CDCl<sub>3</sub>) 8.56 (2H, dd,  $\downarrow$  7.5, 3.7Hz), 8.10 (1H, m), 7.95 (1H, m), 7.88 (2H, d,  $\downarrow$  8.5Hz), 7.80 (1H, m), 7.70 (1H, m), 7.50 (3H, m),  
15 7.23 (2H, d,  $\downarrow$  8.5Hz), 5.05 (1H, m), 4.65 (1H, m), 3.72 (3H, s), 3.49 (1H, m), 3.15 (2H, m), 1.45 (9H, s). m/z (ES<sup>+</sup>, 70V) 499 (MH<sup>+</sup>).

#### INTERMEDIATE 18

20 Methyl (S)-2-Amino-3-[4-[(3-phenyl-1-quinazolinyl)amino]phenyl]propanoate

Intermediate 17 (678mg, 1.36mmol) in EtOAc (30ml) was saturated with HCl gas and stirred for 45 mins. The brown precipitate was filtered off and dried to give the title compound (518mg, 96%) as a brown foamy solid.  $\delta$ H (DMSO d<sub>6</sub>) 9.12 (1H, d,  $\downarrow$  8.6Hz), 8.83 (2H, m), 8.50 (1H, d,  $\downarrow$  8.1Hz), 8.44  
25 (2H, d,  $\downarrow$  7.1Hz), 8.14 (1H, d,  $\downarrow$  8.1Hz), 8.10 (1H, t,  $\downarrow$  8.1Hz), 7.84 (2H, d,  $\downarrow$  8.6Hz), 7.70 (1H, d,  $\downarrow$  7.1Hz), 7.63 (2H, t,  $\downarrow$  7.1Hz), 7.40 (2H, d,  $\downarrow$  8.5Hz), 3.70 (3H, s), 3.67 (1H, m), 3.30 (1H, dd,  $\downarrow$  14.0, 5.5Hz), 3.18 (1H, dd,  $\downarrow$  14.0, 7.4Hz). m/z (ES<sup>+</sup>, 70V) 399 (MH<sup>+</sup>).

30 INTERMEDIATE 19

Ethyl (R)-3-Amino-3-[4-(tert-butoxycarbonyl)aminophenyl]propanoate

Ethyl (3R)-3-{Benzyl[(1S)-1-phenylethyl]amino}-3-[4-(tert-butoxycarbonyl)amino phenyl]propanoate (1.18g, 2.35mmol) was dissolved in MeOH  
35 (10ml) and formic acid (1ml) and 10% palladium on carbon added and the mixture refluxed for 2h. The reaction mixture was cooled, filtered through

Celite® and concentrated to give the crude title compound which was used immediately in the next reaction.  $\delta$ H (CDCl<sub>3</sub>) 7.34 (2H, d,  $\downarrow$  8.1Hz), 7.27 (2H, d,  $\downarrow$  8.1Hz), 7.10 (1H, br s), 4.59 (1H, m), 4.11 (2H, q,  $\downarrow$  7.1Hz), 3.14 (1H, dd,  $\downarrow$  16.8, 7.9Hz), 2.86 (1H, dd,  $\downarrow$  16.8, 12.0Hz), 1.20 (3H, t,  $\downarrow$  7.1Hz).

#### INTERMEDIATE 20

##### Ethyl (R)-3-amino-3-(4-aminophenyl)propanoate

Intermediate 19 was dissolved in EtOAc (25ml) and the solution saturated with HCl gas. The solution was stirred at RT for 90 mins whilst a white precipitate formed. The solid was filtered and dried to give the title compound (570mg, 88% over 2 steps) as a white solid.  $\delta$ H (DMSO d<sub>6</sub>) 8.79 (2H, br s), 7.63 (2H, d,  $\downarrow$  8.4Hz), 7.36 (2H, d,  $\downarrow$  8.4Hz), 4.58 (1H, m), 3.98 (2H, q,  $\downarrow$  7.1Hz), 3.19 (1H, dd,  $\downarrow$  16.3, 5.6Hz), 2.99 (1H, dd,  $\downarrow$  16.3, 9.1Hz), 1.08 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 192 (M-NH<sub>3</sub>).

#### INTERMEDIATE 21

##### Ethyl (R)-3-(4-Aminophenyl)-3-(tert-butoxycarbonylamino)propanoate

Intermediate 20 (550mg, 1.96mmol) was dissolved in dioxan (10ml) and treated with sodium bicarbonate (1g), water (10ml) and di-tert-butyl dicarbonate (427mg) and the mixture stirred for 16 h. Water was added and the product extracted into EtOAc (x 2), washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give the crude product which was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to give the title compound (296mg, 49%) as an oil.  $\delta$ H (CDCl<sub>3</sub>) 7.07 (2H, d,  $\downarrow$  8.3Hz), 6.64 (2H, d,  $\downarrow$  8.3Hz), 5.28 (1H, br s), 4.99 (1H, m), 4.05 (2H, q,  $\downarrow$  7.1Hz), 2.82 (1H, dd,  $\downarrow$  15.1, 6.5Hz), 2.73 (1H, dd,  $\downarrow$  15.1, 6.5Hz), 1.42 (9H, s), 1.17 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 331 (MNa<sup>+</sup>).

#### INTERMEDIATE 22

##### Ethyl (3R)-3-[(tert-Butoxycarbonylamino)]-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propanoate

Intermediate 21 (250mg, 0.81mmol) in 2-ethoxyethanol (2ml) was treated with 1-chloro-2,6-naphthyridine (134mg) and heated at 120° for 15mins, then 100°C for 1h, then cooled and concentrated. The residue was

extracted into EtOAc (x 3), washed with sodium bicarbonate solution, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to give the crude product. The products were purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1-20:1-10:1) to give the deprotected compound (106mg, 30%) as a brown gum and the title compound (98mg, 36%) as a yellow gum.  $\delta$ H (CDCl<sub>3</sub>) 9.18 (1H, s), 8.66 (1H, d,  $\downarrow$  5.9Hz), 8.20 (1H, d,  $\downarrow$  5.8Hz), 7.73 (1H, d,  $\downarrow$  5.9Hz), 7.65 (2H, d,  $\downarrow$  8.5Hz), 7.30 (2H, d,  $\downarrow$  8.5Hz), 7.19 (1H, d,  $\downarrow$  5.8Hz), 5.47 (1H, m), 5.08 (1H, m), 4.09 (2H, q,  $\downarrow$  7.1Hz), 2.83 (2H, t,  $\downarrow$  6.4Hz), 1.44 (9H, s), 1.20 (3H, t,  $\downarrow$  7.1Hz). m/z (ES<sup>+</sup>, 70V) 437 (MH<sup>+</sup>).

### INTERMEDIATE 23

#### Ethyl (R)-3-Amino-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propanoate

Intermediate 22 (100mg, 1mmol) was dissolved in EtOAc (5ml) and saturated with HCl gas. The reaction mixture was stirred to give a precipitate which was filtered and dried to give the title compound which was combined with the material isolated from the previous reaction.  $\delta$ H (CDCl<sub>3</sub>) 9.18 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 7.65 (2H, d,  $\downarrow$  8.5Hz), 7.37 (2H, d,  $\downarrow$  8.5Hz), 7.19 (1H, d,  $\downarrow$  5.7Hz), 4.44 (1H, t,  $\downarrow$  6.8Hz), 4.15 (2H, q,  $\downarrow$  7.1Hz), 2.68 (2H, d,  $\downarrow$  6.8Hz), 1.25 (3H, t,  $\downarrow$  7.1Hz).

### INTERMEDIATE 24

#### N-BOC-O-(2-Pyrimidinyl)-L-tyrosine methyl ester

A solution of N-BOC-L-tyrosine methyl ester (3.0g, 10.2mmol) in DMF (5ml) was added to a suspension of NaH (60% in oil, 11.2mmol, 447mg) in DMF (10ml). After 10 min, a solution of 2-chloropyrimidine (11.2mmol, 1.28g) in DMF (3ml) was added and the mixture stirred overnight. The reaction was quenched with water, diluted EtOAc and washed with water and brine. The EtOAc layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification by column chromatography [SiO<sub>2</sub>, EtOAc/hexane, 1:1] gave the title compound.  $\delta$ H (DMSO d<sub>6</sub>) 8.62 (2H, d,  $\downarrow$  4.8Hz), 7.37 (1H, d,  $\downarrow$  8.1Hz), 7.28 (2H, d,  $\downarrow$  8.4Hz), 7.24 (1H, t,  $\downarrow$  4.8Hz), 7.09 (2H, d,  $\downarrow$  8.4Hz), 4.18 (1H, m), 3.01 (1H, dd,  $\downarrow$  13.8, 4.6Hz), 1.33 (9H, s).

### INTERMEDIATE 25



**O-(2-Pyrimidinyl)-L-tyrosine methyl ester hydrochloride**

Removal of BOC group from Intermediate 24 (HCl/EtOAc) gave the title compound as a white solid.  $\delta$ H (DMSO  $d_6$ ) 8.69 (3H, m), 8.63 (2H, d,  $\downarrow$  4.9Hz), 7.31-7.25 (3H, m), 7.15 (2H, d,  $\downarrow$  8.6Hz), 4.30 (1H, m), 3.69 (3H, s), 3.19 (1H, dd,  $\downarrow$  14.5, 6.4Hz), 3.12 (1H, dd,  $\downarrow$  14.3, 7.2Hz).

**INTERMEDIATE 26****N-BOC-O-(3,5-Dichloroisonicotinoyl)-L-tyrosine methyl ester**

A solution of N-BOC-L-tyrosine methyl ester (2.95g, 10mmol) in THF (10ml) was added to a suspension of NaH (60% in oil, 11mmol, 440mg) in THF (30ml) at 0°. After 10min, a solution of 3,5-dichloroisonicotinoyl chloride (11mmol, 2.32g) in THF (10ml) was added and the mixture stirred at RT for 4h.  $\text{NH}_4\text{Cl}$  (aq) was added and the mixture extracted with DCM. The DCM extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. Recrystallisation (EtOAc/hexane) gave the title compound as white crystals (3.61g, 77%).  $\delta$ H (DMSO  $d_6$ ) 8.89 (2H, s), 7.39 (2H, d,  $\downarrow$  8.5Hz), 7.32 (1H, d,  $\downarrow$  8.2Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 4.21 (1H, m), 3.62 (3H, s), 3.05 (1H, dd,  $\downarrow$  13.8, 4.9Hz), 2.89 (1H, dd,  $\downarrow$  13.8, 10.5Hz), 1.31 (9H).  $m/z$  ( $\text{ES}^+$ , 70V) 410 ( $\text{M}^+ + \text{Na}$ ).

**INTERMEDIATE 27****O-(3,5-Dichloroisonicotinoyl)-L-tyrosine methyl ester hydrochloride**

Intermediate 26 (3.61g) in EtOAc (150ml) was treated with HCl/EtOAc (3m, 50ml). The white precipitate produced was filtered off and dried to give the title compound as a white solid (1.93g).  $\delta$ H (DMSO  $d_6$ ) 8.90 (2H, s), 8.74 (3H, br), 7.42 (2H, d,  $\downarrow$  8.5Hz), 7.28 (2H, d,  $\downarrow$  8.6Hz), 4.31 (1H, m), 3.67 (3H, s), 3.25 (1H, dd,  $\downarrow$  14.2, 6.0Hz), 3.17 (1H, dd,  $\downarrow$  14.1, 7.2Hz).  $m/z$  ( $\text{ES}^+$ , 70V) 369 ( $\text{MH}^+$ ).

**INTERMEDIATE 28****3-Butyl-4-methoxy-3-cyclobutene-1,2-dione**

*n*-BuLi (8.13ml of a 1.6M solution in hexane, 13mmol) was added slowly to a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (1.42g, 10mmol) in THF (100ml) at -78°. After 2h, trifluoroacetic anhydride (2.12ml, 15mmol) was added. After a further 30min the cold solution was poured into  $\text{NH}_4\text{Cl}$ (aq) (100ml) and EtOAc (100ml) and stirred well. The aqueous



layer was extracted with EtOAc. The organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 30:70) gave the title compound as a yellow oil (803mg, 48%).  $\delta$ H (CDCl<sub>3</sub>) 4.42 (3H, s), 2.60 (2H, t,  $\downarrow$  7.6Hz),  
5 1.71-1.61 (2H, m), 1.44-1.32 (2H, m), 0.94 (3H, t,  $\downarrow$  7.3Hz).  $m/z$  (ES<sup>+</sup>, 70V) 169 (MH<sup>+</sup>).

#### INTERMEDIATE 29

##### 10 Methyl (Z)-2-[(tert-butoxycarbonyl)amino]-3-(3-methoxy-4-nitrophenyl)-2-propenoate

Activated manganese IV oxide (26g) was added to a mixture of 3-methoxy-4-nitrobenzylalcohol (5.26g, 28.7mmol), *N*-(*t*-Butyloxycarbonyl)- $\alpha$ -(diethylphosphono)glycine methylester (described in WO99/47547) (8.91g, 27.4mmol) and DBU (4.29ml, 28.7mmol) in DCM (150ml) at 0°. The  
15 mixture was stirred at RT overnight then filtered. The filtrate was washed with dil. HCl, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. Recrystallisation from MeOH gave the title compound as pale brown crystals (4.6g).  $\delta$ H (DMSO *d*<sub>6</sub>) 8.94 (1H, br s), 7.91 (1H, d,  $\downarrow$  8.4Hz), 7.56 (1H, d,  $\downarrow$  1.5Hz), 7.36 (1H, dd,  $\downarrow$  8.5, 1.3Hz), 7.12 (1H, br s), 3.92 (3H, s), 3.75 (3H, s), 1.37  
20 (9H, s).  $m/z$  (ES<sup>+</sup>, 70V) 375 (M<sup>+</sup>+Na).

#### INTERMEDIATE 30

##### 25 Methyl 3-(4-amino-3-methoxyphenyl)-2-[(tert-butoxycarbonyl)amino]-2-propanoate

A mixture of Intermediate 29 (2.30g, 6.53mmol) and palladium on charcoal (10% Pd on carbon, 230mg) in MeOH (65ml) was stirred under a hydrogen atmosphere at RT overnight. The catalyst was filtered off and the filtrate concentrated *in vacuo*. Recrystallisation (Et<sub>2</sub>O/hexane) gave the title compound as dark pink needles (1.62g, 77%).  $\delta$ H (DMSO *d*<sub>6</sub>) 7.12 (1H,  
30 d,  $\downarrow$  7.9Hz), 6.65 (1H, s), 6.51 (2H, s), 4.52 (1H, s), 4.49 (1H, s), 4.07 (1H, m), 3.72 (3H, s), 3.59 (3H, s), 2.81 (1H, dd,  $\downarrow$  13.7, 5.4Hz), 2.69 (1H, dd,  $\downarrow$  13.1, 9.5Hz), 1.32 (9H, s).  $m/z$  (ES<sup>+</sup>, 70V) 347 (MNa<sup>+</sup>).

#### INTERMEDIATE 31

##### 35 Methyl 3-(4-[(6,7-dimethoxy-4-quinazolinyl)amino]-3-methoxyphenyl)-2-[(tert-butoxycarbonyl)amino]propanoate

A mixture of Intermediate 30 (486mg, 1.5mmol), 4-chloro-6,7-dimethoxyquinazoline (337mg, 1.5mmol) and diisopropylethylamine (261 $\mu$ l, 1.5mmol) in ethoxyethanol (1.5ml) was heated at 120° for 24h. The mixture was diluted with DCM, washed with dil. HCl and water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (SiO<sub>2</sub>: MeOH/DCM, 5:95) gave the title compound as a brown gum (720mg, 94%).  $\delta$ H (DMSO d<sub>6</sub>) 9.10 (1H, s, ArNH), 8.34 (1H, d,  $\downarrow$  1.0Hz), 7.85 (1H, d,  $\downarrow$  1.4Hz), 7.47-7.44 (2H, m), 7.40 (1H, d,  $\downarrow$  8.0Hz), 7.47-7.44 (2H, m), 7.40 (1H, d,  $\downarrow$  8.0Hz), 7.20 (1H, s), 7.07 (1H, s), 6.91 (1H, d,  $\downarrow$  8.0Hz), 4.34-4.28 (1H, m), 3.98 (3H, s), 3.98 (3H, s), 3.82 (3H, s), 3.70 (3H, s), 3.09 (1H, dd,  $\downarrow$  13.8, 5.0Hz), 2.95 (1H, dd,  $\downarrow$  13.7, 10.0Hz), 1.42 (9H, s).  $m/z$  (ES<sup>+</sup>, 70V) 573 (MH<sup>+</sup>).

### INTERMEDIATE 32

#### Methyl 2-amino-3-{4-[6,7-dimethoxy-4-quinazolinyl]amino}-3-methoxyphenyl}propanoate hydrochloride

Dry HCl was bubbled into a solution of Intermediate 31 (715mg, 1.4mmol) in EtOAc (30ml) for a few seconds. The mixture was stirred at RT for 1h. The precipitate was filtered off and dried to give the title compound as a brown solid (534mg, 85%).  $\delta$ H (DMSO d<sub>6</sub>, 370K) 8.57 (1H, s), 8.23 (1H br s), 7.43 (1H, d,  $\downarrow$  7.9Hz), 7.15 (1H, s), 6.95 (1H, dd,  $\downarrow$  8.0, 1.5Hz), 4.28 (1H, dd,  $\downarrow$  7.1, 6.2Hz), 4.02 (3H, s), 4.01 (2H, s), 3.82 (3H, s), 3.75 (3H, s), 3.31 (1H, dd,  $\downarrow$  14.2, 6.1Hz), 3.24 (1H, dd,  $\downarrow$  14.2, 7.1Hz).  $m/z$  (ES<sup>+</sup>, 70V) 413 (MH<sup>+</sup>).

### INTERMEDIATE 33

#### Methyl (S)-2-[(tert-butoxycarbonyl)amino]-3-{4-[2-(2,6-dichlorophenyl)ethynyl]phenyl}propanoate

Nitrogen was bubbled through a solution of *N*-BOC-*L*-4-iodophenylalanine methyl ester (1.50g, 3.69mmol) in toluene (20ml) and triethylamine (10ml). Bis(triphenylphosphine)palladium (II) chloride (10mol%, 260mg) and copper (I) iodide (20mol%, 140mg) were added. A solution of 2,6-dichlorophenylacetylene (949mg, 5.55mmol) in toluene (10ml) was added by syringe-pump over 3h. The mixture was stirred at RT for a further 3h. The mixture was diluted with EtOAc, washed with dil. HCl and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. Column chromatography (SiO<sub>2</sub>;

EtOAc/hexane, 20:80) gave the title compound as a brown gum (1.61g, 97%).  $\delta$ H (DMSO  $d_6$ ), 7.60-7.58 (2H, m), 7.51 (2H, d,  $\downarrow$  8.1Hz), 7.42 (1H, dd,  $\downarrow$  8.8, 7.4Hz), 7.33 (2H, d,  $\downarrow$  8.1Hz), 4.21 (1H, br m), 3.73 (3H, s), 3.04 (1H, dd,  $\downarrow$  13.8, 5.0Hz), 2.88 (1H, dd,  $\downarrow$  13.7, 10.0Hz) and 1.31 (9H, s):  $m/z$  (ES<sup>+</sup>, 70V) 470 ( $M^+$  + Na).

#### INTERMEDIATE 34

##### Methyl (S)-2-amino-3-(4-[2-(2,6-dichlorophenyl)ethynyl]phenyl)propanoate hydrochloride

10 HCl gas was bubbled through a solution of the compound of Example 33 (1.6g, 3.57mmol) in EtOAc (70ml) for 5 min. The mixture was stirred for 1h at RT. The precipitate formed was filtered off and washed with ether to give the title compound as an off-white solid (1.21g, 88%).  $\delta$ H (DMSO  $d_6$ ), 8.73 (3H, br s), 7.60 (2H, d,  $\downarrow$  8.0Hz), 7.56 (2H, d,  $\downarrow$  8.1Hz), 7.44 (1H, dd,  $\downarrow$  8.7, 7.6Hz), 7.35 (2H, d,  $\downarrow$  8.1Hz), 4.30 (1H, t,  $\downarrow$  6.6Hz), 3.68 (3H, s), 3.25 (1H, dd,  $\downarrow$  14.2, 6.1Hz), 3.16 (1H, dd,  $\downarrow$  14.0, 7.2Hz);  $m/z$  (ES<sup>+</sup>, 70V) 348 ( $M^+$  + H).

#### INTERMEDIATE 35

##### 5-Methyl-4-[3H]quinazolinone

20 6-Methylantranilic acid (5g, 33mmol) and formamidine acetate (0.4g, 41mmol) were refluxed in 2-ethoxyethanol (50ml) for 16h. On cooling the solvent was removed *in vacuo*, the residue slurried in diethyl ether, the solid filtered, washed with diethyl ether and dried to yield 3.6g of the title compound.  $\delta$ H (DMSO  $d_6$ ), 7.97 (1H, s), 7.60 (1H, dd,  $\downarrow$  7.9, 7.6Hz), 7.43 (1H, d,  $\downarrow$  8.0Hz), 7.21 (1H, d,  $\downarrow$  7.3Hz), 2.76 (3H, s);  $m/z$  (ES<sup>+</sup> 70V) 161 (MH<sup>+</sup>).

#### INTERMEDIATE 36

##### 4-Chloro-5-methylquinazoline

30 The compound of Intermediate 35 (4.1g, 26mmol) was refluxed in phosphorous oxychloride (60ml) for 5h. On cooling the phosphorous oxychloride was removed *in vacuo* and the residue quenched in ice cold saturated sodium bicarbonate. The resulting mixture was extracted with EtOAc (3 x 50ml), washed with brine, dried ( $Mg_2SO_4$ ), the solvent removed and the residue purified by column chromatography (silica 1:1

ethylacetate/ isohexane) to yield the title compound as white solid.  $\delta$ H (DMSO  $d_6$ ), 8.5 (1H, s), 7.7 (1H, dd) 7.8 (1H, d), 7.3 (1H, m)

### INTERMEDIATE 37

5 Ethyl-(S)-3-{4-[(5-methyl -4-quinazolinyl)amino]phenyl}-2-(t-butoxy-carbonyl)amino propanoate

Ethyl-(S)-3-(4-aminophenyl)-2-[(t-butoxycarbonyl)amino]propanoate (413mg, 1.4mmol) and Intermediate 36 (250mg, 1.4mmol) were heated at reflux in EtOH (10ml). The solution was cooled, solvent removed *in vacuo*,  
10 residue stirred in EtOAc (10ml) and sat. sodium bicarbonate (10ml), organic layer isolated, washed with sodium bicarbonate, brine, dried (MgSO<sub>4</sub>) and the solvent removed, to yield the title compound as an off white solid (520mg).  $\delta$ H (CDCl<sub>3</sub>) 8.6 (1H, s), 7.8 (1H, br, s), 7.7 (1H, d,  $\downarrow$  7.8Hz), 7.6 (2H, m), 7.3 (1H, d,  $\downarrow$  7.2Hz), 7.2 (2H, d,  $\downarrow$  8.7Hz), 5.2 (1H, br m),  
15 4.6 (1H, br m) 4.2 (2H, q,  $\downarrow$  7.2Hz), 3.15 (2H, br m), 3.1 (3H, s), 1.4 (9H, s), 1.25 (3H, t,  $\downarrow$  7.2Hz).

### INTERMEDIATE 38

20 Ethyl-(S)-3-(4-[(5-methyl-4-quinazolinyl)amino]phenyl)-2-aminopropanoate

The compound of Intermediate 37 (1.1g, 2.5mmol) in DCM (4ml) and trifluoroacetic acid (2ml) was stirred for 1h. The solution was poured onto saturated sodium bicarbonate and extracted with EtOAc (x 3). The extracts were washed with brine, dried (MgSO<sub>4</sub>), solvent removed *in vacuo* to give the title compound as yellow oil.  $\delta$ H (CDCl<sub>3</sub>), 8.6 (1H, s),  
25 7.8 (1H, br s), 7.7 (1H, d,  $\downarrow$  8.4Hz), 7.6 (3H, m), 7.3 (3H, m) 4.2 (2H, q,  $\downarrow$  7.2Hz), 3.7 (1H, m), 3.1 (1H, dd,  $\downarrow$  13.6, 8.4Hz), 3.0 (1H, s), 2.8 (1H, dd,  $\downarrow$  13.6, 7.9Hz), 1.3 (3H, t,  $\downarrow$  7.2Hz).  $m/z$  (ES<sup>+</sup>, 70V) 351 (MH<sup>+</sup>)

30 INTERMEDIATE 39

Methyl-2-amino-5-(trifluoromethoxy)benzoate

A mixture of 2-Bromo-4-trifluoromethoxy aniline (2.7g, 10.6mmol) palladium (II) acetate (360mg,) triethylamine (9ml) and 1,3-bis (diphenylphosphino) propane (651mg) in anhydrous methanol (10ml) and  
35 anhydrous dimethyl formamide (10ml) were cooled in ice/methanol bath, and carbon monoxide gas was bubbled through for 10min. The mixture

was heated at 70° under a partially inflated balloon of carbon monoxide for 17h. On cooling nitrogen was bubbled through the solution to disperse excess carbon monoxide, and the mixture was poured onto water (50ml) and EtOAc (50ml), filtered through Celite®, the organic layer isolated, and aqueous phase was extracted with EtOAc. The organic layers were combined, washed with water (x 2), brine (x 2), dried (MgSO<sub>4</sub>), and the solvent removed *in vacuo*. The residue was distilled and the fraction boiling at 170°, 0.08 mbar collected to yield 1.8g of a yellow liquid.  $\delta$ H (CDCl<sub>3</sub>), 7.7 (1H, m), 7.1 (1H, m), 6.6 (1H, d,  $\downarrow$  9.0Hz), 3.9 (3H, s).

10

**INTERMEDIATE 40****6-(Trifluoromethoxy)-4[3H]-quinazoline.**

Prepared in a similar manner to the compound of intermediate 35 from the compound of Intermediate 39.  $\delta$ H (DMSO d<sub>6</sub>), 8.1 (1H, s), 7.9 (1H, s), 7.8 (2H, m).

15

**INTERMEDIATE 41****4-Chloro-6-(trifluoromethoxy)quinazoline.**

Prepared from the compound of Intermediate 40 in a similar manner to that described for Intermediate 36.  $\delta$ H (CDCl<sub>3</sub>), 9.1 (1H, s), 8.1 (1H, d,  $\downarrow$  9.2Hz), 8.0 (1H, m), 7.8 (1H, m); m/z (EI<sup>+</sup>, 70V) 249/251.

20

**INTERMEDIATE 42****Ethyl-(S)-3-(4-{[6-(trifluoromethoxy)-4-quinazolinyl]amino}phenyl)-2-[(t-butoxycarbonyl)amino]propanoate**

25

Prepared from Intermediate 41 in a similar manner to that described for Intermediate 37.  $\delta$ H (CDCl<sub>3</sub>), 8.7 (1H, s), 8.0 (1H, d,  $\downarrow$  9.1Hz), 7.8 (1H, br s), 7.6 (3H, m), 7.2 (2H, d,  $\downarrow$  8.5Hz), 5.0 (1H, br s), 4.5 (1H, br s), 4.2 (2H, q,  $\downarrow$  7.2Hz), 3.1 (2H, br s), 1.4 (9H, s), 1.2 (3H, t,  $\downarrow$  7.2Hz).

30

**INTERMEDIATE 43****Ethyl (S)-3-(4-{[6-trifluoromethoxy)-4-quinazolinyl]amino}phenyl)-2-aminopropanoate**

Prepared from the compound of Intermediate 42 in a similar manner to that described for Intermediate 38.  $\delta$ H (CDCl<sub>3</sub>), 8.7 (1H, s), 7.9 (1H, d,  $\downarrow$  9.2Hz), 7.7 (1H, br m), 7.6 (3H, m), 7.2 (2H, d,  $\downarrow$  7.1Hz), 4.2 (2H, q,  $\downarrow$

35

7.2Hz), 3.8 (1H, m), 3.1 (1H, m), 2.9 (1H, m), 1.3 (3H, t,  $\downarrow$  7.2Hz); m/z (EI<sup>+</sup>, 70V) 421 (MH<sup>+</sup>)

#### INTERMEDIATE 44

##### 5 3-Amino-4-methoxy-3-cyclobutene-1,2-dione

3,4-Dimethoxy-3-cyclobutene-1, 2-dione (1.3g, 9.2mmol) in of MeOH (10.0ml) was treated with aqueous ammonia (10.0ml of a 2.0M solution) and stirred at ambient temperature for 2h. The yellow precipitate thus formed was recovered by filtration, washed with MeOH and Et<sub>2</sub>O and dried  
10 *in vacuo* to afford the title compound (0.87g, 75%) as an amorphous yellow powder  $\delta$ H (d<sup>6</sup> DMSO) 8.32 (2H, br s), 4.28 (3H, s). m/z (ES<sup>+</sup>, 70V) 127 (MH<sup>+</sup>).

#### INTERMEDIATE 45

##### 15 Methyl-(S)-3-{4-[(2-chloro-6,7-dimethoxy-4-quinazolinyl)amino]phenyl}-2-[(t-butoxycarbonyl)amino]propanoate

Prepared in a similar manner to the compound of Intermediate 9 from methyl-(S)-3-(4-aminophenyl)-2-(N-t-butoxycarbonylamino)propanoate and 2,4-dichloro-6,7-dimethoxyquinazoline.  $\delta$ H (CD<sub>3</sub>OD) 7.72 (1H, s), 7.69  
20 (2H, d,  $\downarrow$  8.4Hz), 7.25 (2H, d,  $\downarrow$  8.4Hz), 7.05 (1H, s), 4.34 (1H, m), 4.15 (2H, m,  $\downarrow$  7.1Hz), 4.00 (3H, s), 3.96 (3H, s), 3.08 (1H, m), 2.97 (1H, m), 1.40 (9H, s), 1.23 (3H, t,  $\downarrow$  7.1Hz). m/z (ESI<sup>+</sup> 531 (MH<sup>+</sup>).

#### EXAMPLE 1

##### 25 Ethyl (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-isopropoxy-3,4-dioxocyclobut-1-enylamino)propanoate

A solution of Intermediate 3 (2.1g, 5mmol) in EtOH (25ml) was treated with DIPEA (0.96ml, 5.5mmol) and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (1.1g, 5.5mmol) and heated to reflux for 16h. The reaction mixture was  
30 cooled and concentrated *in vacuo*. The residue was taken up in EtOAc (50ml) and washed with 10% aqueous citric acid (2 x 50ml), NaHCO<sub>3</sub> solution (2 x 30ml) and brine (30ml), dried (MgSO<sub>4</sub>) and the solvent evaporated *in vacuo* to give a pale yellow oil, which was purified by column chromatography (SiO<sub>2</sub>, EtOAc:hexane 1:1) to give the title compound as a  
35 white foam 1.62g, 62%).  $\delta$ H (DMSO d<sup>6</sup>), 10.45 (1H, s), 8.69 (2H, s), 8.52 (1H, d,  $\downarrow$  8.4Hz), 7.57 (2H, d,  $\downarrow$  7.6Hz), 7.25 (2H, d,  $\downarrow$  7.6Hz), 5.22 (1H,

m), 4.69 (1H, m), 4.19 (2H, q,  $\downarrow$  7.1Hz), 3.25 (1H, dd,  $\downarrow$  14.3, 5.2Hz), 3.07 (1H, dd,  $\downarrow$  14.3, 9.4Hz), 1.38 (6H, dd,  $\downarrow$  6.2, 3.9Hz), 1.23 (3H, t,  $\downarrow$  7.1Hz).

## EXAMPLE 2

5 Ethyl-(S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-[3-methoxypropylamino]-3,4-dioxocyclobut-1-enylamino)propanoate

A solution of the compound of Example 1 (1.55g, 2.99mmol) in EtOH (25ml) was treated with 3-methoxypropylamine (0.34 ml, 3.3mmol) and stirred for 16h at RT. The white solid was isolated by filtration, and  
10 washed with cold Et<sub>2</sub>O (3 x 10ml) to give the title compound (1.38g, 84%).  $\delta$ H (DMSO d<sub>6</sub>), 10.89 (1H, s), 8.80 (2H, s), 7.59 (2H, d,  $\downarrow$  8.4Hz), 7.25 (2H, br m), 7.18 (2H, d,  $\downarrow$  8.4Hz), 4.99 (1H, m), 4.18 (2H, q,  $\downarrow$  7.1Hz), 3.54 (2H, m), 3.37 (2H, t,  $\downarrow$  6.3Hz), 3.23 (3H, s), 3.16 (1H, m), 3.06 (1H, m), 1.75 (2H, q,  $\downarrow$  6.3Hz), 1.22 (3H, t,  $\downarrow$  7.1Hz).  $m/z$  (ES<sup>+</sup>, 70V) 549 (MH<sup>+</sup>).

15

## EXAMPLE 3

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-methoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

A solution of the compound of Example 2 (1.30g, 2.48mmol) in THF (40ml) and water (25ml) was treated with LiOH.H<sub>2</sub>O (125mg, 2.98mmol) and stirred for 3h at RT. The reaction mixture was concentrated *in vacuo*, and acidified to pH 2 with 1M hydrochloric acid. The resulting solid was isolated by filtration, washed with water and dried *in vacuo* to give the title compound (1.15g, 85%).  $\delta$ H (DMSO d<sub>6</sub>), 10.89 (1H, s), 8.79 (2H, s), 7.58 (3H, m), 7.19 (2H, d,  $\downarrow$  8.1Hz), 4.92 (1H, m), 3.54 (2H, m), 3.23 (3H, s), 3.16 (1H, dd,  $\downarrow$  13.9, 5.1Hz), 3.05 (1H, dd,  $\downarrow$  13.9, 7.4Hz) and 1.74 (2H, t,  $\downarrow$  6.4Hz).  $m/z$  (ES<sup>+</sup>, 70V) 521 (MH<sup>+</sup>).

25

## EXAMPLE 4

30 Ethyl-(S)-3[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate

A solution of the compound of Example 1 (1g, 1.93mmol) in EtOH (25ml) was treated with n-propylamine (0.18ml, 2.12mmol) and stirred at RT for 16h. The resulting white solid was isolated by filtration and washed with cold Et<sub>2</sub>O (2 x 20ml) to give the title compound (0.68g, 68%).  $\delta$ H (DMSO d<sub>6</sub>), 10.87 (1H, s), 8.78 (2H, s), 7.57 (4H, m.), 7.16 (2H, d,  $\downarrow$  8.3Hz), 4.97

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(1H, m), 4.16 (2H, q,  $\downarrow$  7.1Hz), 3.44 (2H, m), 3.11 (2H, m), 1.50 (2H, m), 1.20 (3H, t,  $\downarrow$  7.1Hz), 0.86 (3H, t,  $\downarrow$  7.1Hz).  $m/z$  (ES<sup>+</sup>, 70V) 519 (MH<sup>+</sup>).

#### EXAMPLE 5

5 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid.

The title compound (0.67g, 99%) was prepared from the compound of Example 4 (0.66g, 1.27mmol) in a similar manner to the compound of Example 3.  $\delta$ H (DMSO d<sub>6</sub>), 10.51 (1H, s), 8.71 (2H, s), 7.56 (2H, d,  $\downarrow$  8.3Hz), 7.36 (1H, m), 7.31 (1H, d,  $\downarrow$  9.0Hz), 7.22 (2H, d,  $\downarrow$  8.3Hz), 4.96  
10 (1H, m), 3.49 (2H, q,  $\downarrow$  6.7Hz), 3.20 (1H, dd,  $\downarrow$  14.1, 5.6Hz), 3.09 (1H, dd,  $\downarrow$  14.1, 7.4Hz), 1.57 (2H, m), 0.92 (3H, t,  $\downarrow$  7.4Hz).  $m/z$  (ES<sup>+</sup>, 70V) 491 (MH<sup>+</sup>).

15 EXAMPLE 6

Ethyl (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-[(2-tert-butyl)-3,4-dioxo-1-cyclobutenylamino]propanoate

A mixture of the compound of Intermediate 4 (392mg, 2mmol), Intermediate 3 (837mg, 2mmol) and DIPEA (348 $\mu$ l, 2mmol) in abs. ethanol  
20 (20ml) was heated at reflux for 24h. The solvent was removed *in vacuo* and the residue dissolved in DCM, washed with HCl (1M), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. Column chromatography (SiO<sub>2</sub>; MeOH/DCM, 5:95) gave the title compound as a yellow foam (741mg, 72%).  $\delta$ H (DMSO d<sub>6</sub>), 10.83 (1H, s), 8.77 (2H, s), 8.54 (1H, d,  $\downarrow$  8.6Hz), 7.54 (2H, d,  $\downarrow$  8.4Hz), 7.23 (2H, d,  $\downarrow$  8.5Hz), 5.01 (1H, m), 4.17 (2H, q,  $\downarrow$  7.1Hz), 3.25  
25 (1H, dd,  $\downarrow$  4.6Hz), 3.04 (1H, dd,  $\downarrow$  13.7, 10.9Hz), 1.21 (9H, s), 1.21 (3H, t,  $\downarrow$  7.1Hz).  $m/z$  (ES<sup>+</sup>, 70V) 518 (M<sup>+</sup> + H).

#### EXAMPLE 7

30 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[(2-tert-butyl)-3,4-dioxo-1-cyclobutenylamino]propanoate

Lithium hydroxide monohydrate (66mg, 1.56mmol) was added to the compound of Example 6 (735mg, 1.42mmol) in THF (14ml) and water (14ml). After 2.5h at RT the THF was removed *in vacuo*. The aqueous  
35 residue was acidified (pH1, 1M HCl) and the precipitate filtered off, washed with water and dried to give the title compound as a pale brown solid



(625mg, 90%).  $\delta$ H (DMSO  $d_6$ ), 13.29 (1H, br s), 10.85 (1H, s), 8.78 (2H, s), 8.49 (1H, d,  $\downarrow$  9.2Hz), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.24 (2H, d,  $\downarrow$  8.5Hz), 4.95 (1H, ddd,  $\downarrow$  11.0, 9.3, 4.2Hz), 3.28 (1H, dd,  $\downarrow$  13.8, 4.1Hz), 3.04 (1H, dd,  $\downarrow$  13.7, 1.1Hz), 1.22 (9H, s);  $m/z$  (ES<sup>+</sup>, 70V) 490 ( $M^+$  + H).

5

**EXAMPLE 8****Methyl (S)-3-[4-[(3,5-dichloroisonicotinoyl)oxy]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

10 In a similar manner to that described for Example 1 and Example 2 the title compound was prepared from the compound of Intermediate 27 as a white solid.  $\delta$ H (DMSO  $d_6$ , 390K) 8.81 (2H, s), 7.36 (2H, d,  $\downarrow$  8.7Hz), 7.26 (2H, d,  $\downarrow$  8.7Hz), 5.11-5.05 (1H, m), 3.78 (3H, s), 3.52-3.47 (2H, m) 3.29 (1H, dd,  $\downarrow$  14.2, 5.9Hz), 3.18 (1H, dd,  $\downarrow$  14.2, 9.7Hz), 1.63-1.54 (2H, m), 0.93 (3H, t,  $\downarrow$  7.4Hz).  $m/z$  (ES<sup>+</sup>, 70V) 506 (MH<sup>+</sup>).

15

**EXAMPLE 9****(S)-3-[4-[(3,5-Dichloroisonicotinoyl)oxy]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20 In a similar manner to that described for Example 3 the title compound was prepared from Example 8 as a white solid.  $\delta$ H (DMSO  $d_6$ , 390K) 13.31 (1H, br), 8.80 (2H, s), 7.38 (2H, d,  $\downarrow$  8.6Hz), 7.25 (2H, d,  $\downarrow$  8.6Hz), 5.0-4.98 (1H, m), 3.52-3.47 (2H, m,) 3.29 (1H, dd,  $\downarrow$  14.2, 5.7Hz), 3.16 (1H, dd,  $\downarrow$  14.2, 7.5Hz), 2.51-2.50 (2H, m), 0.93 (3H, t,  $\downarrow$  7.4Hz).  $m/z$  (ES<sup>+</sup>, 70V) 494 (MH<sup>+</sup>).

25

**EXAMPLE 10****Ethyl (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-butyl-3,4-dioxo-1-cyclobutenylamino)propanoate**

30 A mixture of Intermediate 28 (336mg, 2mmol), Intermediate 3 (837mg, 2mmol) and DIPEA (700 $\mu$ l, 4mmol) in EtOH (2ml) was heated at reflux for 2h. The solvent was removed *in vacuo*. The residue was dissolved in DCM (150ml), washed with dil. HCl, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (SiO<sub>2</sub>: MeOH/DCM, 5:95) gave the title compound as a yellow foam (904mg, 87%).  $\delta$ H (DMSO  $d_6$ , 390K) 10.39  
35 (1H, br s), 8.68 (2H, s), 8.59 (1H, br d,  $\downarrow$  7.8Hz), 7.55 (2H, br s), 7.26 (2H, d,  $\downarrow$  8.3Hz), 4.84 (1H, br s), 4.21 (2H, q,  $\downarrow$  7.1Hz), 3.28 (1H, dd,  $\downarrow$  14.3,

5.3Hz), 3.10 (1H, dd,  $\downarrow$  14.3, 9.2Hz), 2.5 (2H, m), 1.62-1.54 (2H, m), 1.38-1.29 (2H), 1.24 (3H, t,  $\downarrow$  7.1Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 0.91 (3H, t,  $\downarrow$  7.3Hz).  $m/z$  (ES<sup>+</sup>, 70V) 518 (MH<sup>+</sup>).

5 **EXAMPLE 11**

**(S)-3-{4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl}-2-(2-butyl-3,4-dioxo-1-cyclobutenylamino)propanoic acid**

In a similar manner to that described for Example 3 the title compound was prepared from the compound of Example 10 as a pale yellow solid.  $\delta$ H (DMSO d<sub>6</sub>, 370K), 10.48 (1H, s), 8.70 (2H, s), 8.5 (1H, v br), 7.55 (2H, d,  $\downarrow$  7.8Hz), 7.25 (2H, d,  $\downarrow$  7.9Hz), 4.85 (1H, v br), 3.29-3.22 (1H, m), 3.09-3.03 (1H, m), 2.5 (2H, m), 1.57-1.51 (2H, m), 1.36-1.27 (2H, m), 0.90 (3H, t,  $\downarrow$  7.3Hz).  $m/z$  (ES<sup>+</sup>, 70V) 490 (MH<sup>+</sup>).

15 **EXAMPLE 12**

**Ethyl (S)-3-{4-[(2,6-naphthyridin-1-yl)amino]phenyl}-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate**

A solution of Intermediate 7 (280mg, 0.84mmol) and 3,4-diisopropoxy-3-cyclobuten-1,2-dione (200mg, 1.01mmol) in absolute ethanol (5ml) was stirred at RT for 8h then at 50° for 18h. The volatiles were removed *in vacuo* and the residue chromatographed (silica, 80% EtOAc/Hexane to 100% EtOAc) affording the title compound as a dull yellow foam (250mg, 63%).  $\delta$ H (CDCl<sub>3</sub>) 9.18 (1H, s), 8.66 (1H, d,  $\downarrow$  5.9Hz), 8.21 (1H, d,  $\downarrow$  5.7Hz), 7.72 (1H, d,  $\downarrow$  5.9Hz), 7.66 (2H, d,  $\downarrow$  8.5Hz), 7.22 (1H, obs. s), 7.20 (1H, d,  $\downarrow$  5.7Hz), 7.14 (2H, d,  $\downarrow$  8.5Hz), 6.37, 5.90, 5.18 and 4.60 (together 1H, br m's), 4.27 (2H, q,  $\downarrow$  7.1Hz), 3.31-3.10 (2H, br m), 1.42 (3H, d,  $\downarrow$  6.2Hz), 1.41 (3H, d,  $\downarrow$  6.2Hz), 1.32 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 475 (MH<sup>+</sup>).

30 **EXAMPLE 13**

**Ethyl (S)-3-{4-[(2,6-naphthyridin-1-yl)amino]phenyl}-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoate**

The compound of Example 12 (240mg, 0.51mmol) and diethylamine (74mg, 105 $\mu$ l, 1.01mmol) in absolute ethanol (2ml) was stirred at 45° under an atmosphere of N<sub>2</sub> for 18h. The volatiles were removed *in vacuo* and the residue chromatographed (silica, gradient elution 1 to 3%

EtOH/EtOAc) to afford the title compound as a yellow foam (240mg, 97%).  $\delta$ H (CDCl<sub>3</sub>) 9.17 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.19 (1H, d,  $\downarrow$  5.7Hz), 7.78 (1H, d,  $\downarrow$  5.9Hz), 7.68 (2H, d,  $\downarrow$  8.4Hz), 7.48 (1H, s), 7.18 (1H, d,  $\downarrow$  5.7Hz), 7.13 (2H, d,  $\downarrow$  8.4Hz), 5.45-5.35 (2H, overlapping signals), 4.25 (2H, q,  $\downarrow$  7.1Hz), 3.68-3.31 (4H, br m), 3.30-3.18 (2H, m), 1.31 (3H, t,  $\downarrow$  7.1Hz), 1.22 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 488 (MH<sup>+</sup>).

#### EXAMPLE 14

##### 10 (S)-3-{4-[(2,6-Naphthyridin-1-yl)amino]phenyl}-2-[(2-N,N-diethylamino)-3,4-dioxocyclobut-1-enyl]amino}propanoic acid

The compound of Example 13 (230mg, 0.47mmol) was treated with a solution of LiOH.H<sub>2</sub>O (25ml, 0.60mmol) in water (4ml) and dioxan (4ml) at RT for 1.5h. A few drops of AcOH were added and the volatiles removed *in vacuo*. The residue was chromatographed [silica, gradient elution, DCM (200 to 120), MeOH (20), AcOH (3), H<sub>2</sub>O (2)] to afford the product as a yellow oil. Freeze-drying from aqueous MeOH afforded the title compound as a bright yellow amorphous solid (165mg, 76%).  $\delta$ H (d<sub>6</sub> DMSO) 9.28 (1H, s), 9.20 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.37 (1H, d,  $\downarrow$  5.8Hz), 8.12 (1H, d,  $\downarrow$  5.8Hz), 7.78 (2H, d,  $\downarrow$  8.5Hz), 7.66 (1H, d,  $\downarrow$  9.0Hz), 7.26 (1H, d,  $\downarrow$  5.8Hz), 7.22 (2H, d,  $\downarrow$  8.5Hz), 5.15-5.05 (1H, m), 3.70-3.30 (4H, br m), 3.22 (1H, dd,  $\downarrow$  13.9, 4.0Hz), 3.00 (1H, dd,  $\downarrow$  13.9, 10.9Hz), 1.09 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

#### EXAMPLE 14A

##### 25 (S)-3-{4-[(2,6-Naphthyridin-1-yl)amino]phenyl}-2-[(2-N,N-diethylamino)-3,4-dioxocyclobut-1-enyl]amino}propanoic acid, sodium salt

A solution of the compound of Example 14 (250mg, 0.55mmol) in water (3ml) and THF (2ml) was treated with sodium hydroxide solution (0.1M, 5.5mmol) and stirred for 10mins. The solution was freeze dried to give the title compound as a bright orange solid (250mg, 95%).  $\delta$ H (d<sub>6</sub> DMSO) 8.43 (1H, s), 8.06 (2H, s), 7.48 (1H, d,  $\downarrow$  5.6Hz), 7.16 (2H, d,  $\downarrow$  8.3Hz), 6.93 (2H, d,  $\downarrow$  8.4Hz), 5.88 (1H, d,  $\downarrow$  5.6Hz), 3.73 (1H, t,  $\downarrow$  6.7Hz), 3.88-3.83 (2H, m), 3.55-3.50 (2H, m), 2.86 (1H, dd,  $\downarrow$  13.3, 6.5Hz), 2.67 (1H, m), 1.12 (6H, t,  $\downarrow$  7.1Hz). (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

In a similar manner to that described for Examples 13 and 14 were prepared the Examples 15 to 28:

**EXAMPLE 15**

5 **Ethyl (S)-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]-2-[2-(piperidin-1-yl)-3,4-dioxocyclobut-1-enylamino]propanoate**

$\delta_H$  (CDCl<sub>3</sub>) 9.18 (1H, s), 8.67 (1H, d,  $\downarrow$  5.9Hz), 8.20 (1H, d,  $\downarrow$  5.9Hz), 7.74 (1H, d,  $\downarrow$  5.9Hz), 7.67 (2H, d,  $\downarrow$  8.5Hz), 7.35 (1H, s), 7.20 (1H, d,  $\downarrow$  5.9Hz), 7.13 (2H, d,  $\downarrow$  8.5Hz), 5.40 (2H, narrow m), 4.25 (2H, q,  $\downarrow$  7.2Hz), 3.69-3.50 (4H, br m), 3.22 (2H, narrow m), 1.67 (6H, narrow m), 1.31 (3H, t,  $\downarrow$  7.2Hz);  $m/z$  (ES<sup>+</sup>, 70V) (MH<sup>+</sup>) 500.

10

**EXAMPLE 16**

15 **(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(piperidin-1-yl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO) 9.29 (1H, s), 9.21 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.38 (1H, d,  $\downarrow$  5.9Hz), 8.12 (1H, d,  $\downarrow$  5.8Hz), 7.77 (2H, d,  $\downarrow$  8.4Hz), 7.76 (1H, obs. signal), 7.26 (1H, d,  $\downarrow$  5.8Hz), 7.21 (2H, d,  $\downarrow$  8.4Hz), 5.07 (1H, narrow m), 3.72-3.48 (4H, br m), 3.20 (1H, dd,  $\downarrow$  14.0, 4.1Hz), 2.98 (1H, dd,  $\downarrow$  14.0, 10.6Hz), 1.68-1.49 (6H, br m);  $m/z$  (ES<sup>+</sup>, 70V) (MH<sup>+</sup>) 472.

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**EXAMPLE 17**

25 **Ethyl (S)-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

$\delta_H$  (CDCl<sub>3</sub>) 9.18 (1H, s), 8.70 (1H, d,  $\downarrow$  5.9Hz), 8.15 (1H, s), 7.85 (1H, br s), 7.64 (2H, d,  $\downarrow$  8.3Hz), 7.19-7.13 (3H, m), 5.40-5.30 (1H, m), 4.35-4.20 (2H, m), 3.60-3.10 (6H, m), 1.65-1.55 (4H, m), 1.33 (3H, t,  $\downarrow$  7.1Hz), 0.9 (6H, t,  $\downarrow$  7.35Hz);  $m/z$  (ES<sup>+</sup>, 70V) MH<sup>+</sup> 516.

30 **EXAMPLE 18**

**(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO, 370K) 9.19 (1H, s), 9.0 (1H, br s), 8.64 (1H, d,  $\downarrow$  8.6Hz), 8.34 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 7.79 (2H, d,  $\downarrow$  8.4Hz), 7.25-7.21 (1H, m), 7.23 (2H, d,  $\downarrow$  8.7Hz), 7.05 (1H, br s), 5.15 (1H, br s), 3.56-

35

3.40 (4H, m), 3.27 (1H, dd,  $\downarrow$  14.2, 4.9Hz), 3.10 (1H, dd,  $\downarrow$  14.2, 9.4Hz), 1.65-1.50 (4H, m), 0.86 (6H, t,  $\downarrow$  7.3Hz),  $m/z$  (ES<sup>+</sup>, 70V) MH<sup>+</sup> 488.

#### **EXAMPLE 19**

5 **(S)-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]-2-(2-tert-butyl-3,4-dioxocyclobut-1-enylamino)-propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO) 9.29 (1H, s), 9.22 (1H, s), 8.67 (1H, d,  $\downarrow$  5.8Hz), 8.51 (1H, d,  $\downarrow$  9.1Hz), 8.40 (1H, d,  $\downarrow$  0.8Hz), 8.38 (1H, d,  $\downarrow$  0.8Hz), 8.13 (1H, dd,  $\downarrow$  5.6, 1.3Hz), 7.78 (2H, nr m), 7.26 (1H, d,  $\downarrow$  5.8Hz), 7.19 (1H, d,  $\downarrow$  8.6 Hz),  
10 4.95 (1H, br s), 3.4-3.2 (1H, m), 3.04 (1H, dd,  $\downarrow$  13.6, 11.1Hz), 1.23 (9H, s).  
 $m/z$  (ES<sup>+</sup>, 70V) (MH<sup>+</sup>) 445.2.

#### **EXAMPLE 20**

15 **(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-N-methyl-N-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO, 390K) 9.19 (1H, s), 9.08 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 7.78 (2H, d,  $\downarrow$  8.3Hz), 7.25-7.20 (3H, m), 5.06 (1H, br s), 3.58-3.42 (2H, m), 3.24 (1H, dd,  $\downarrow$  14.1, 4.7Hz), 3.16 (3H, s), 3.06 (1H, dd,  $\downarrow$  14.1, 9.5Hz), 1.54-1.50 (2H, m),  
20 1.27 (2H, dd,  $\downarrow$  15.1, 7.4Hz), 0.87 (3H, t,  $\downarrow$  7.31Hz).  $m/z$  ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).

#### **EXAMPLE 21**

25 **(S)-3-[4-(2,6-Naphthyridin-1-yl-N-methylamino)phenyl]-2-[2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO, 350K) 9.23 (1H, d,  $\downarrow$  1.0Hz), 8.36 (1H, d,  $\downarrow$  5.6Hz), 8.22 (1H, d,  $\downarrow$  6.0Hz), 7.49 (1H, dd,  $\downarrow$  5.7, 0.9Hz), 7.30 (1H, br d,  $\downarrow$  8.0Hz), 7.21 (2H, d,  $\downarrow$  8.5Hz), 7.05 (1H, d,  $\downarrow$  6.0Hz), 6.93 (2H, d,  $\downarrow$  8.5Hz), 5.12-5.09 (1H, narrow m), 3.66-3.45 (4H, m), 3.49 (3H, s), 3.24 (1H, dd,  $\downarrow$  14.0-4.5Hz),  
30 3.03 (1H, dd,  $\downarrow$  14.0, 10.1Hz), 1.10 (6H, t,  $\downarrow$  7.1Hz)  $m/z$  (ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).

#### **EXAMPLE 22**

35 **(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[(2,5-dimethyl-3-pyrrolin-1-yl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

5  $\delta$ H (DMSO  $d_6$ , 350K); 9.19 (1H, d,  $\downarrow$  0.9Hz), 9.09 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 7.78 (2H, d,  $\downarrow$  8.3Hz), 7.26-7.18 (4H, m), 5.90 (2H, s), 5.09 (1H, br s), 4.85 (2H, q,  $\downarrow$  12.8, 6.4Hz), 3.27 (1H, dd,  $\downarrow$  14.1, 4.8Hz), 3.11 (1H, dd,  $\downarrow$  14.1, 9.5Hz), 1.35 (3H, d,  $\downarrow$  6.4Hz), 1.31 (3H, d,  $\downarrow$  6.4Hz),  $m/z$  (ES<sup>+</sup>, 70V) 484 (MH<sup>+</sup>).

**EXAMPLE 23****(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(N-methyl-N-propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10  $\delta$ H (DMSO  $d_6$ , 350K), 9.20 (1H, s), 9.10 (1H, s), 8.65 (1H, d,  $\downarrow$  5.85Hz), 8.35 (1H, d,  $\downarrow$  5.92Hz), 8.14 (1H, d,  $\downarrow$  5.68Hz), 7.79 (2H, d,  $\downarrow$  8.03Hz), 7.36 (1H, d,  $\downarrow$  9.0Hz), 7.26-7.22 (3H, m), 5.16 (1H, br s), 3.50-3.39 (2H, m), 3.25 (1H, dd,  $\downarrow$  14.09, 4.83Hz), 3.17 (3H, s), 3.07 (1H, dd,  $\downarrow$  14.1, 9.9Hz), 1.61-1.52 (2H, m), 0.84 (3H, t,  $\downarrow$  7.35Hz);  $m/z$  (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

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**EXAMPLE 24****(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[(2-(S)-(2-methoxymethyl)pyrrolidin-1-yl)-3,4-dioxocyclobut-1-enyl]amino]propanoic acid**

20  $\delta$ H (DMSO  $d_6$ , 350K) 9.20 (1H, s), 9.10 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 7.80 (2H, d,  $\downarrow$  8.3Hz), 7.27-7.20 (4H, m), 5.07 (1H, br s), 4.20 (1H, d,  $\downarrow$  5.2Hz), 3.85-3.64 (2H, m), 3.35-3.32 (2H, m), 3.25 (3H, s), 3.25-3.01 (2H, m), 2.03-1.75 (4H, m);  $m/z$  (ES<sup>+</sup>, 70V), 502 (MH<sup>+</sup>).

25

**EXAMPLE 25****(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(N-ethyl-N-isopropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

30  $\delta$ H (DMSO  $d_6$ , 350K); 9.20 (1H, s), 9.09 (1H, s), 8.64 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.15 (1H, d,  $\downarrow$  5.7Hz), 7.78 (2H, d,  $\downarrow$  8.3Hz), 7.26-7.20 (4H, m), 5.18 (1H, br s), 4.44-4.37 (1H, m), 3.45 (2H, q,  $\downarrow$  7.2, 2.4Hz), 3.25 (1H, dd,  $\downarrow$  14.1, 4.7Hz), 3.08 (1H, dd,  $\downarrow$  14.1, 9.8Hz), 1.20 (6H, q,  $\downarrow$  6.7, 3.3Hz), 1.14 (3H, t,  $\downarrow$  7.1Hz),  $m/z$  (ES<sup>+</sup>, 70V), 474 (MH<sup>+</sup>).

35 **EXAMPLE 26**



**(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(N-methyl-N-iso-propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

5  $\delta$ H (DMSO  $d_6$ , 350K) 9.20 (1H, s), 9.09 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.6Hz), 7.79 (2H, d,  $\downarrow$  8.3Hz), 7.38 (1H, d,  $\downarrow$  8.1Hz), 7.26-7.22 (3H, m), 5.12 (1H, br s), 4.46-4.40 (1H, m), 3.25 (1H, dd,  $\downarrow$  14.1, 4.8Hz), 3.05 (1H, dd,  $\downarrow$  14.2, 4.6Hz), 3.06 (3H, s), 1.82 (3H, d,  $\downarrow$  2.58Hz, 1.65 (3H, d,  $\downarrow$  2.6Hz);  $m/z$  (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

**EXAMPLE 27**

10 **(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(2,5-dimethylpyrrolidin-1-yl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15  $\delta$ H (DMSO  $d_6$ , 350K) 9.20 (1H, d,  $\downarrow$  0.9Hz), 9.10 (1H, s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.35 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 7.79 (2H, d,  $\downarrow$  8.3Hz), 7.26-7.23 (3H, m), 3.26 (1H, dd,  $\downarrow$  14.2, 4.8Hz), 3.1 (1H, dd,  $\downarrow$  14.2, 9.7Hz), 2.15-2.09 (2H, m), 1.73-1.66 (2H, m), 1.28 (3H, d,  $\downarrow$  6.4Hz), 1.25 (3H, d,  $\downarrow$  6.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 486 (MH<sup>+</sup>).

**EXAMPLE 28**

20 **(S)-3-[4-(2,6-Naphthyridin-1-ylamino)phenyl]-2-[2-(2-methylpiperidin-1-yl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

25  $\delta$ H (DMSO  $d_6$ , 370K), 9.19 (1H, s), 9.03 (1H, s), 8.64 (1H, d,  $\downarrow$  5.8Hz), 8.33 (1H, d,  $\downarrow$  5.9Hz), 8.14 (1H, d,  $\downarrow$  5.6Hz), 7.78 (2H, q,  $\downarrow$  8.4, 2.3Hz), 7.25-7.22 (4H, m), 5.13 (1H, br s), 4.45 (1H, br s), 4.04 (1H, d,  $\downarrow$  13.7Hz), 3.25-3.20 (2H, m), 3.11-3.05 (1H, m), 1.76-1.49 (6H, m), 1.24 (3H, q,  $\downarrow$  6.9, 5.2Hz);  $m/z$  (ES<sup>+</sup>, 70V) 486 (MH<sup>+</sup>).

**EXAMPLE 29**

30 **Methyl (S)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]-2-[2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino]propanoate**

To methyl (S)-2-(2-isopropoxy-3,4-dioxocyclobut-1-enylamino)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]-propanoate (prepared from the compound of Intermediate 8 in a similar manner to the compound of Example 1) (0.20g, 0.44mmol) in methanol (3ml) was added 2 equivalents of diethylamine (0.09ml) and the solution was stirred at 65° overnight. The solution was cooled and then evaporated. The solid was chromatographed (silica,

EtOAc/ isohexane 50-100%) to afford the title compound (0.15g, 73%) as a white solid.  $\delta_H$  ( $CDCl_3$ ) 9.30 (1H, s), 8.77 (1H, d,  $\downarrow$  5.7Hz), 8.19 (1H, d,  $\downarrow$  5.8Hz), 8.08 (1H, d,  $\downarrow$  5.79Hz), 7.44 (1H, d,  $\downarrow$  5.8Hz), 7.24-7.18 (4H, m), 5.46 (1H, m), 5.35 (1H, m), 3.83 (3H, s), 3.70-3.40 (4H, br s), 3.31 (2H, d,  $\downarrow$  5.3Hz), 1.24 (6H, t,  $\downarrow$  7.2Hz).  $m/z$  ( $ES^+$ , 70V)  $MH^+$  475.

### EXAMPLE 30

#### (S)-3-[4-(2,6-Naphthyridin-1-yloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

The compound of Example 29 (0.137g, 0.29mmol) in dioxan (2ml) and water (2ml) was treated with LiOH.H<sub>2</sub>O (0.02g) and stirred at RT for 4h, a few drops of glacial acetic acid were added and the solution was then evaporated *in vacuo*. The product was chromatographed (silica; DCM 200 : MeH 20 : HOAc 3 : H<sub>2</sub>O 2) to afford the title compound as an off-white solid (0.10g, 78%).  $\delta_H$  ( $d_6$  DMSO, 350K), 9.40 (1H, s), 8.76 (1H, d,  $\downarrow$  5.7Hz), 8.15-8.09 (2H, m), 7.65 (1H, dd,  $\downarrow$  5.8, 0.9Hz), 7.37 (1H, s), 7.36 (2H, d,  $\downarrow$  8.6Hz), 7.20 (2H, d,  $\downarrow$  8.6Hz), 5.15 (1H, br s), 3.59-3.51 (4H, m), 3.32 (1H, dd,  $\downarrow$  14.1, 4.8Hz), 3.13 (1H, dd,  $\downarrow$  14.1, 9.9Hz), 1.14 (6H, t,  $\downarrow$  7.1Hz).  $m/z$  ( $ES^+$ , 70V)  $MH^+$  461.

20

The compounds of Examples 31 to 33 were prepared in a similar manner to the compounds of Examples 29 and 30.

### EXAMPLE 31

#### (S)-3-[4-(2,6-Naphthyridin-1-yloxy)phenyl]-2-[2-piperidin-1-yl]-3,4-dioxocyclobut-1-enylamino]propanoic acid.

$\delta_H$  ( $d_6$  DMSO, 370K) 9.39 (1H, s), 8.76 (1H, d,  $\downarrow$  5.7Hz), 8.13 (2H, nr m), 7.65 (1H, dd,  $\downarrow$  5.7, 0.9Hz), 7.34 (2H, d,  $\downarrow$  8.6Hz), 7.21 (2H, d,  $\downarrow$  8.6Hz), 5.16 (1H, br s), 3.64-3.59 (5H, m), 3.31 (1H, dd,  $\downarrow$  14.1, 5.0Hz), 3.12 (1H, dd,  $\downarrow$  14.1, 9.6 Hz), 1.63-1.57 (5H, m);  $m/z$  ( $ES^+$ , 70V)  $MH^+$  473.

30

### EXAMPLE 32

#### Methyl-(S)-3-[4-(2,6-naphthyridin-1-yloxy)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

$\delta_H$  ( $d_6$  DMSO) 9.41 (1H, s), 8.76 (1H, d,  $\downarrow$  5.7Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 8.07 (1H, d,  $\downarrow$  5.7Hz), 7.74 (1H, d,  $\downarrow$  8.9Hz), 7.67 (1H, d,  $\downarrow$  5.8Hz), 7.33

35



(2H, d,  $\downarrow$  8.5Hz), 7.18 (2H, d,  $\downarrow$  8.5Hz), 5.23 (1H, m), 3.72 (3H, s), 3.37 (5H, br m), 3.11 (1H, m), 1.48 (4H, br m), 0.80 (6H, t,  $\downarrow$  7.3Hz).

### EXAMPLE 33

5 **(S)-3-[4-(2,6-Naphthyridin-1-yloxy)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  ( $d_6$  DMSO 350K) 9.41 (1, d,  $\downarrow$  1.0Hz), 8.77 (1H d,  $\downarrow$  8.7Hz), 8.14 (1H, d,  $\downarrow$  5.7Hz), 8.11 (1H, d,  $\downarrow$  5.7Hz), 7.67 (1H, dd,  $\downarrow$  5.8, 0.9Hz), 7.35 (2H, d,  $\downarrow$  8.6Hz), 7.27 (1H, d,  $\downarrow$  8.9Hz), 7.21 (2H, d,  $\downarrow$  8.6Hz), 5.20 (1H, m), 3.47  
10 (4H, m), 3.33 (1H, dd,  $\downarrow$  14.1, 4.8Hz), 3.13 (1H, dd,  $\downarrow$  14.1, 10.0Hz), 1.55 (4H, m), 0.86 (6H, t,  $\downarrow$  7.4Hz).  $m/z$  ( $ES^+$ , 70V) 489 ( $MH^+$ ).

### EXAMPLE 34

15 **Methyl-(S)-3-[4-[2-(2,6-dichlorophenyl)ethynyl]phenyl]-2-[(2-isopropoxy-3,4-dioxo-1-cyclobutenyl)amino]propanoate**

A mixture of the compound of Intermediate 34 (1.17g, 3.04mmol), 3,4-diisopropoxy-3-cyclobutene-1,2-diene (632mg, 3.19mmol) and DIPEA (540 $\mu$ l, 3.1mmol) in MeOH (30ml) was stirred at RT for 3 days. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with  
20 dil. HCl, dried ( $Na_2SO_4$ ) and evaporated *in vacuo*. Column chromatography ( $SiO_2$ ; MeOH/DCM, 3:97) gave the title compound as a yellow gum (1.45g, 98%).  $\delta_H$  (DMSO  $d_6$ , 390K), 8.47 (1H, d,  $\downarrow$  7.9Hz), 7.53-7.50 (3H, m), 7.38 (1H, dd,  $\downarrow$  8.7, 7.5Hz), 7.33 (2H, d,  $\downarrow$  8.2Hz), 5.21 (1H, sept.  $\downarrow$  6.2Hz), 4.78-4.72 (1H, m), 3.72 (3H, s), 3.31 (1H, dd,  $\downarrow$  14.2, 5.2Hz), 3.13 (1H, dd,  $\downarrow$  14.2, 9.4Hz), 1.38 (3H, d,  $\downarrow$  6.1Hz). 1.37 (3H, d,  $\downarrow$   
25 6.2Hz);  $m/z$  ( $ES^+$ , 70V) 486 ( $M^+ + H$ ).

### EXAMPLE 35

30 **Methyl-(S)-3-[4-[2-(2,6-dichlorophenyl)ethynyl]phenyl]-2-[2-propylamino-3,4-dioxocyclobut-1-enylamino]propanoate**

Propylamine (96 $\mu$ l, 1.18mmol) was added to a solution of the compound of Example 34 (475mg, 0.98mmol) in MeOH (10ml). The reaction mixture was stirred at RT overnight. Volatiles were removed *in vacuo* and the resulting solid triturated with boiling MeOH. The solid was filtered off to  
35 give the title compound as a white solid (335mg, 71%).  $\delta_H$  (DMSO- $d_6$ , 390K) 7.57-7.53 (4H, m), 7.44-7.40 (1H, m), 7.33 (2H, d,  $\downarrow$  8.3Hz), 7.3

(1H, br m) 7.2 (1H, br m), 5.10 (1H, m), 3.76 (3H, s), 3.54-3.49 (2H, m), 3.30 (1H, dd,  $\downarrow$  14.1, 5.9Hz), 3.18 (1H, dd,  $\downarrow$  14.1, 7.7Hz), 1.60 (2H, sept.  $\downarrow$  7.1Hz), 0.95 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 485 ( $M^+$  +H).

5 **EXAMPLE 36**

**(S)-3-{4-[2-(2,6-Dichlorophenyl)ethynyl]phenyl}-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Lithium hydroxide monohydrate (34mg, 0.81mmol) was added to the compound of Example 35 (325mg, 0.671mmol) in a mixture of THF (7ml) and water (7ml). After 1h at RT the THF was removed *in vacuo*. The aqueous residue was acidified (pH 1-2, dil. HCl) and the precipitated filtered off, washed with water and dried to give the title compound as a yellow solid (315mg, 90%).  $\delta$ H (DMSO  $d_6$ , 390K), 7.37-7.31 (4H, m), 7.21 (1H, dd,  $\downarrow$  8.6, 7.5Hz), 7.14 (2H, d,  $\downarrow$  8.4Hz), 7.1 (2H, br m), 4.82 (1H, m), 15 3.33-3.29 (2H, m), 3.11 (1H, dd,  $\downarrow$  14.1, 5.7Hz), 2.98 (1H, dd,  $\downarrow$  14.1, 7.6Hz), 1.39 (2H, sept.  $\downarrow$  7.1Hz), 0.75 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 471 ( $M^+$  +H).

**EXAMPLE 37**

20 **Methyl (S)-3-{4-[2-(2,6-dichlorophenyl)ethynyl]phenyl}-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

A mixture of the compound of Example 34 (470mg, 0.969mmol) and diethylamine (401 $\mu$ l, 3.88mmol) in MeOH (10ml) was heated at 50°C overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO<sub>2</sub>; MeOH/DCM, 5:95) to give the title compound as a light brown foam (450mg, 93%).  $\delta$ H (DMSO  $d_6$ , 390K), 7.55-7.50 (4H, m), 7.42-7.35 (3H, m), 7.16 (1H, d,  $\downarrow$  8.5Hz), 5.63 (1H, m), 3.74 (3H, s), 3.55 (4H, q,  $\downarrow$  7.1Hz), 3.34 (1H, dd,  $\downarrow$  14.2, 5.3Hz), 3.20 (1H, dd,  $\downarrow$  14.2, 9.4Hz), 1.17 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 499 ( $M^+$  +H).

30

**EXAMPLE 38**

**(S)-3-{4-[2-(2,6-Dichlorophenyl)ethynyl]phenyl}-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Obtained as an off-white solid from the compound of Example 37 by ester hydrolysis using the method described above for Example 36.  $\delta$ H (DMSO- $d_6$ , 390K), 7.42-7.37 (4H, m), 7.29-7.24 (3H, m), 6.91 (1H, br d,  $\downarrow$  8.7Hz), 35

3.43 (4H, q,  $\downarrow$  7.1Hz), 3.22 (1H, dd,  $\downarrow$  14.2, 5.1Hz), 3.06 (1H, dd,  $\downarrow$  14.2, 9.4Hz), 1.04 (6H, t  $\downarrow$  7.1Hz).  $m/z$  (ES<sup>+</sup>, 70V) 485 ( $M^+$  +H).

5 The compounds of Examples 39 to 44 were prepared from methyl-(S)-3-(4-aminophenyl)-2-(*N*-t-butyloxycarbonylamino)propanoate and the appropriate reagent in a similar manner to that described for Intermediate 3 then derivatised in a manner analogous to that described for Examples 1, 2 and 3.

10 **EXAMPLE 39**

**(S)-3-[4-(Benzylcarboxamido)phenyl]-2-(2-*n*-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15  $\delta_H$  (d<sub>6</sub> DMSO 390K); 9.25 (1H, s), 7.86 (1H, s), 7.44 (2H, d,  $\downarrow$  8.4Hz), 7.40-7.15 (5H, m), 7.08 (2H, d,  $\downarrow$  8.4Hz), 7.0 (1H, d,  $\downarrow$  8.0Hz), 4.94 (1H, br s), 3.62 (2H, s), 3.47 (2H, nr m), 3.14 (1H, dd,  $\downarrow$  14.1, 5.7Hz), 3.04 (1H, dd,  $\downarrow$  14.1, 6.8Hz), 1.57 (2H, dd,  $\downarrow$  14.3, 7.1Hz), 0.92 (3H, t,  $\downarrow$  7.3Hz);  $m/z$  (ES<sup>+</sup>, 70V) 436 (MH<sup>+</sup>).

**EXAMPLE 40**

20 **(S)-3-[4-(2,4,6-Trifluorobenzylamino)phenyl]-2-(2-*n*-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO 390K) 7.88 (1H, s), 7.12 (1H, br s), 6.97 (1H, br s), 6.92 (2H, d,  $\downarrow$  8.3Hz), 6.78 (2H, nr m), 6.58 (2H, d,  $\downarrow$  8.3Hz), 4.89 (1H, br s), 4.27 (2H, s), 3.46-3.48 (2H, nr m), 3.04 (1H, dd,  $\downarrow$  14.18, 5.7Hz), 2.95 (1H, 25 dd,  $\downarrow$  14.2, 6.68Hz), 1.62-1.53 (2H, Nr m), 0.92 (3H, t,  $\downarrow$  7.38Hz);  $m/z$  (ES<sup>+</sup>, 70V), 462 (MH<sup>+</sup>).

**EXAMPLE 41**

30 **(S)-3-[4-(2,6-Dichlorobenzylamino)phenyl]-2-(2-*n*-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  (d<sub>6</sub> DMSO) 7.26 (2H, s), 7.17 (1H, d,  $\downarrow$  7.3Hz), 7.14 (1H, br s), 6.95 (1H, br s), 6.8 (2H, d,  $\downarrow$  8.4Hz), 6.5 (2H, d,  $\downarrow$  8.47Hz), 4.70 (1H, br s), 4.31 (3H, s), 3.13 (2H, m), 2.89 (1H, dd,  $\downarrow$  14.2, 5.6Hz), 2.79 (1H, dd,  $\downarrow$  14.2, 7.1Hz), 2.85 (1H, br s), 1.44 (2H, dd,  $\downarrow$  14.2, 7.1Hz), 0.76 (3H, t,  $\downarrow$  7.4Hz); 35  $m/z$  (ES<sup>+</sup>, 70V) 476 (MH<sup>+</sup>).

**EXAMPLE 42****(S)-3-[4-(2,4,6-Trichlorobenzylamino)phenyl]-2-(2-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

5  $\delta_H$  ( $d_6$  DMSO) 7.55 (2H, s), 7.23 (1H, br s), 7.09 (1H, br d,  $\downarrow$  8.4Hz), 6.96 (2H, d,  $\downarrow$  8.4Hz), 6.66 (2H, d,  $\downarrow$  8.5Hz), 4.90 (1H, br s), 4.44 (2H, s), 3.48 (2H, m), 3.07 (1H, dd,  $\downarrow$  14.1, 5.5Hz), 2.95 (1H, dd,  $\downarrow$  14.2, 7.2Hz), 1.60 (2H, dd,  $\downarrow$  14.3, 7.0Hz), 0.93 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  ( $ES^+$ , 70V) 509 ( $MH^+$ ).

**EXAMPLE 43**

10 **(S)-3-[4-(3-Chlorothiophen-2-ylcarboxamido)phenyl]-2-(2-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  ( $d_6$  DMSO) 9.50 (1H, s), 7.79 (1H, d,  $\downarrow$  5.2Hz), 7.57 (2H, d,  $\downarrow$  8.4Hz), 7.21 (2H, d,  $\downarrow$  8.4Hz), 7.12 (1H, br s), 7.11 (1H, d,  $\downarrow$  5.2Hz), 4.96 (1H, br s), 3.49 (2H, m), 3.25-3.02 (2H, m), 1.59 (2H, dd,  $\downarrow$  14.3, 7.1Hz), 0.93 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  ( $ES^+$ , 70V) 461 ( $MH^+$ ).

15

**EXAMPLE 44****(S)-3-[4-(3-Chlorobenzo[b]thiophen-2-ylcarboxamido)phenyl]-2-(2-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20  $\delta_H$  ( $d_6$  DMSO, 400K) 9.98 (1H, s), 8.07 (1H, nr, m), 7.94 (1H, nr m), 7.6 (5H, m), 7.23 (2H, d,  $\downarrow$  8.4Hz), 7.1 (1H, br s), 4.98 (1H, br s), 3.5 (2H, m), 2.35 (1H, dd,  $\downarrow$  14.2, 5.7Hz), 3.3 (1H, dd,  $\downarrow$  14.2, 5.7Hz), 1.59 (2H, hex,  $\downarrow$  7.3Hz), 0.94 (3H, t,  $\downarrow$  7.3Hz).  $m/z$  ( $ES^+$ , 70V) 512 ( $MH^+$ ).

The compounds of Examples 45 to 47 were prepared from methyl (S)-3-(4-aminophenyl)-2-(N-t-butoxycarbonylamino)propanoate and the appropriate reagent in a similar manner to that described for Intermediate 6 then derivatised in a similar manner to that described for Examples 11, 13 and 14.

25

30 **EXAMPLE 45**

**(S)-3-[4-(Pyrimidin-2-ylamino)phenyl]-2-(2-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  ( $d_6$  DMSO, 390K) 8.86 (1H, br s), 8.41 (2H, d,  $\downarrow$  4.8Hz), 7.64 and 7.62 (2H, dd,  $\downarrow$  1.8, 1.4Hz), 7.15 (1H, br s), 7.12 (2H, d,  $\downarrow$  8.6Hz), 6.77 (1H, t,  $\downarrow$  4.8Hz), 4.93 (1H, br s), 3.48 (2H, t,  $\downarrow$  6.8Hz), 3.18 (1H, dd,  $\downarrow$  14.1,

35

5.5Hz), 3.05 (1H, dd,  $\downarrow$  14.2, 7.3Hz), 1.58 (2H, dd,  $\downarrow$  14.2, 7.0Hz), 0.92 (3H, t,  $\downarrow$  7.4Hz),  $m/z$  (ES<sup>+</sup>, 70V) 396 (MH<sup>+</sup>).

**EXAMPLE 46**

5 **(S)-3-[4-[(2-Benzyl-6-chloropyrimidin-4-yl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid**

$\delta$ H (DMSO, 370K) 9.40 (1H, s), 7.48 (2H, d  $\downarrow$  2.3Hz), 7.38 (4H, s), 7.35-7.25 (2H, m), 7.24 (2H, d,  $\downarrow$  8.5Hz), 6.64 (1H, s), 5.15 (1H, br s), 4.07 (2H, s), 3.60 (2H, q,  $\downarrow$  7.2, 4.7Hz), 3.30 (1H, dd,  $\downarrow$  14.2, 4.9Hz), 3.10 (1H, dd,  $\downarrow$  14.1, 9.4Hz), 1.2 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 534 (MH<sup>+</sup>).

**EXAMPLE 47**

15 **(S)-3-[4-(Quinolin-4-ylamino)phenyl]-2-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

$\delta$ H (DMSO, 390K) 8.48 (1H, d,  $\downarrow$  5.2Hz), 8.39 (1H, d,  $\downarrow$  7.1Hz), 7.93 (1H, dd,  $\downarrow$  8.4, 0.8Hz), 7.71 (1H, d,  $\downarrow$  5.4Hz), 7.54-7.50 (1H, m), 7.32 (2H, d,  $\downarrow$  8.4Hz), 7.24 (2H, d,  $\downarrow$  8.5Hz), 6.83 (1H, d,  $\downarrow$  5.2Hz), 4.68 (1H, m), 3.70-3.50 (4H, m), 3.32 and 3.29 (1H, dd,  $\downarrow$  13.8, 5.5Hz), 3.24 and 3.21 (1H, dd,  $\downarrow$  13.8, 6.3Hz), 1.23 (6H, t,  $\downarrow$  7.2Hz),  $m/z$  (ES<sup>+</sup>, 70V), 459 (MH<sup>+</sup>).

20

The compounds of Examples 48 to 55 were prepared from *N*-BOC-*L*-tyrosine methyl ester and the appropriate reagent in the manner described for Intermediate 24 then derivatised in a manner analogous to that described for Examples 12 to 14.

25

**EXAMPLE 48**

30 **Methyl (S)-3-[4-(2,6-Dichlorobenzyloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

$\delta$ H (DMSO *d*<sub>6</sub>) 7.71 (1H, d,  $\downarrow$  9.0Hz), 7.55-7.52 (2H, m), 7.47-7.42 (1H, d), 7.18 (2H, d,  $\downarrow$  8.7Hz), 6.95 (2H, d,  $\downarrow$  8.7Hz), 5.17 (2H, s), 5.15 (1H, m), 3.70 (3H, s), 3.55 (4H, br), 3.20 (1H, dd,  $\downarrow$  4.6Hz), 3.01-2.93 (1H, m), 1.07 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 505 (MH<sup>+</sup>).

**EXAMPLE 49**

35 **(S)-3-[4-(2,6-Dichlorobenzyloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta$ H (DMSO  $d_6$ ) 13.08 (1H, br), 8.31-8.24 (2H, m), 8.22-8.04 (1H, m), 8.02 (2H, d,  $\downarrow$  8.8Hz), 7.77 (2H, d,  $\downarrow$  8.7Hz), 6.07 (2H, s), 7.70 (1H, br), 5.95 (1H, br m), 4.49-4.40 (4H, m), 4.05 (1H, dd,  $\downarrow$  14.3, 5.1Hz), 3.89 (1H, dd,  $\downarrow$  14.2, 9.1Hz), 1.97 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 491 (MH<sup>+</sup>).

5

**EXAMPLE 50****Methyl (S)-3-[4-(2,6-dichlorobenzyloxy)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

10  $\delta$ H (DMSO  $d_6$ ) 7.60 (1H, br), 7.56 (2H, m), 7.47-7.42 (1H, m), 7.09 (2H, d,  $\downarrow$  8.3Hz), 6.97 (2H, d,  $\downarrow$  8.7Hz), 5.17 (2H, s), 4.99 (1H, m), 3.70 (3H, s), 3.70 (2H, m), 3.12 (1H, dd,  $\downarrow$  5.2 partly obscured), 1.54-1.47 (2H, m), 0.86 (3H, t,  $\downarrow$  7.4Hz).  $m/z$  (ES, 70V) 491 (MH<sup>+</sup>).

**EXAMPLE 51**

15 **(S)-3-[4-(2,6-Dichlorobenzyloxy)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta$ H (DMSO  $d_6$ , 390K), 7.42-7.40 (2H, m), 7.35-7.31 (1H, m), 7.09 (1H, br), 7.08-7.06 (2H, m), 6.89-6.86 (2H, m), 5.17 (2H, s), 4.82 (1H, br), 3.39-3.38 (2H, m), 3.09 (1H, dd,  $\downarrow$  14.2, 5.6Hz), 2.96 (1H, dd,  $\downarrow$  14.2, 7.4Hz), 1.52-  
20 1.47 (2H, m), 0.84 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 477 (MH<sup>+</sup>).

**EXAMPLE 52****Methyl (S)-3-[4-(2-pyrimidinylloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

25  $\delta$ H (DMSO  $d_6$ , 390K) 8.60 (2H, d,  $\downarrow$  4.8Hz), 7.31 (2H, d,  $\downarrow$  8.6Hz), 7.20 (1H, t,  $\downarrow$  4.8Hz), 7.10 (2H, d,  $\downarrow$  8.6Hz), 5.28-5.23 (1H, m), 3.74 (3H, s), 3.56 (4H, q,  $\downarrow$  7.1Hz), 3.31 (1H, dd,  $\downarrow$  14.3, 5.4Hz), 3.17 (1H, dd,  $\downarrow$  14.2, 9.2Hz), 1.17 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 425 (MH<sup>+</sup>).

30 **EXAMPLE 53**

**(S)-3-[4-(2-Pyrimidinylloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta$ H (DMSO  $d_6$ , 390K) 13.10 (1H, br), 8.60 (2H, d,  $\downarrow$  4.8Hz), 7.31 (2H, d,  $\downarrow$  8.7Hz), 7.20 (1H, d,  $\downarrow$  4.8Hz), 7.09 (2H, d,  $\downarrow$  8.7Hz), 6.97 (1H, br), 5.18-  
35 5.17 (1H, m), 3.60-3.59 (4H, m), 3.31 (1H, dd,  $\downarrow$  14.3, 5.2Hz), 3.16 (1H, dd,  $\downarrow$  14.3, 9.1Hz);  $m/z$  (ES<sup>+</sup>, 70V), 411 (MH<sup>+</sup>).



**EXAMPLE 54****Methyl (S)-3-[4-(2-pyrimidinylloxy)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

5  $\delta$ H (DMSO  $d_6$ , 390K) 8.61 (2H, d,  $\downarrow$  4.8Hz), 7.70 (1H, br), 7.55 (1H, br), 7.26-7.19 (3H, m), 7.10 (2H, d,  $\downarrow$  8.5Hz), 5.02 (1H, m), 3.71 (3H, s), 3.44 (2H, br), 3.18 (1H, dd,  $\downarrow$  14.0, 5.4Hz,  $CH_AH_BAr$ ), 3.08 (1H, dd,  $\downarrow$  14.0, 8.0Hz,  $CH_AH_BAr$ ), 1.54-1.46 (2H, m,  $NHCH_2CH_2CH_3$ ), 0.86 (3H, t,  $\downarrow$  7.4,  $NCH_2CH_2CH_3$ );  $m/z$  (ES<sup>+</sup>, 70V) 411 (MH<sup>+</sup>).

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**EXAMPLE 55****(S)-3-[4-(2-Pyrimidinylloxy)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15  $\delta$ H (DMSO  $d_6$ , 390K) 8.67 (2H, d,  $\downarrow$  4.8Hz), 7.33 (2H, d,  $\downarrow$  8.6Hz), 7.27 (1H, d,  $\downarrow$  4.7Hz), 7.16 (2H, d,  $\downarrow$  8.6Hz), 5.06-5.02 (1H, m), 3.58-3.53 (2H, m), 3.31 (1H, dd,  $\downarrow$  14.3, 5.6Hz), 3.18 (1H, dd,  $\downarrow$  14.2, 7.5Hz), 1.67-1.62 (2H, m), 0.99 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 397 (MH<sup>+</sup>).

**EXAMPLE 56**

20 **Methyl (S)-3-[4-[(3-phenyl-1-quinazolinyl)amino]phenyl]-[2-isopropoxy-3,4-dioxocyclobut-1-enyl]amino]propanoate**

Intermediate 18 (518mg, 1.3mmol) was dissolved in MeOH (5ml) and DIPEA base (0.5ml), treated with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (309mg) and stirred at RT for 16h. The solution was concentrated, dissolved in DCM (20ml), washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography (SiO<sub>2</sub>:CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1) to give the title compound (550mg, 1.0mmol, 79%) as a brown foamy solid.  $\delta$ H (DMSO) 8.44 (1H, m), 8.43 (2H, m), 7.80 (2H, m), 7.75 (2H, m), 7.50 (2H, m), 7.49 (2H, m), 7.33 (2H, d,  $\downarrow$  8.6Hz), 5.23 (1H, septet,  $\downarrow$  6.2Hz), 4.80 (1H, m), 3.76 (3H, s), 3.30 (1H, dd,  $\downarrow$  14.2, 5.3Hz), 3.13 (1H, dd,  $\downarrow$  14.2, 9.3Hz), 1.38 (3H, d,  $\downarrow$  6.2Hz), 1.37 (3H, d,  $\downarrow$  6.2Hz);  $m/z$  (ESI, 70V) 537 (MH<sup>+</sup>).

30

**EXAMPLE 57**

35 **Methyl (S)-3-[4-[(2-phenyl-4-quinazolinyl)amino]phenyl]-[2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl]amino]propanoate**

The compound of Example 56 (550mg, 1.0mmol) and diethylamine (0.21ml) in MeOH (5ml) was stirred at RT for 16h and the solution then concentrated. The residue was purified by column chromatography (SiO<sub>2</sub>; DCM/MeOH 100:1) to give the title compound (375mg, 0.68mmol, 68%) as a brown foamy solid.  $\delta$ H (DMSO, 390K) 8.45 (3H, m), 7.85 (4H, m), 7.56 (1H, m), 7.48 (3H, m), 7.35 (2H, d,  $\downarrow$  8.7Hz), 5.33 (1H, m), 3.76 (3H, s), 3.56 (2H, q,  $\downarrow$  7.2Hz), 3.54 (2H, q,  $\downarrow$  7.2Hz), 3.33 (1H, dd,  $\downarrow$  14.2, 5.3Hz), 3.20 (1H, dd,  $\downarrow$  14.2, 9.2Hz), 1.17 (6H, t,  $\downarrow$  7.1Hz); m/z; (ES<sup>+</sup>, 70V) 550 (MH<sup>+</sup>).

10 **EXAMPLE 58**

**(S)-3-[4-[(2-Phenyl-4-quinazolinyl)amino]phenyl]-[2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

Example 57 (360mg, 0.66mol) was dissolved in THF (2ml) and water (2ml) and treated with lithium hydroxide (41mg). The solution was stirred at RT or 90 mins and concentrated. The residue was dissolved in water and slowly acidified to pH2 with dilute hydrochloric acid to give a yellow precipitate which was filtered and dried to give the title compound (237mg, 67%).  $\delta$ H (DMSO d<sub>6</sub>) 9.75 (1H, br m), 8.60 (1H, d,  $\downarrow$  8.7Hz), 8.43 (2H, m), 7.92 (4H, m), 7.62 (1H, m), 7.52 (3H, m), 7.38 (2H, d,  $\downarrow$  8.6Hz), 5.21 (1H, m), 3.57 (2H, q,  $\downarrow$  7.1Hz), 3.55 (2H, q,  $\downarrow$  7.1Hz), 3.3 (1H, dd,  $\downarrow$  14.1, 4.6Hz), 3.15 (1H, dd,  $\downarrow$  14.1, 10.1Hz), 1.14 (3H, t,  $\downarrow$  7.1Hz); m/z (ES<sup>+</sup>, 70V) 536 (MH<sup>+</sup>).

The compounds of Examples 59 to 64 were prepared from methyl-(S)-3-(4-aminophenyl)-2-(N-t-butoxycarbonyl)aminopropanoate and the appropriate quinazoline in a manner similar to that described for Intermediate 18 and then derivatised in a manner similar to that described for Examples 56, 57 and 58.

30 **EXAMPLE 59**

**Methyl-(S)-3-[4-(Quinazolin-4-ylamino)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta$ H (CDCl<sub>3</sub>) 8.73 (1H, s), 8.0 (1H, d,  $\downarrow$  8.5Hz), 7.91 (1H, d,  $\downarrow$  8.3Hz), 7.83-7.54 (6H, m), 7.15 (2H, d,  $\downarrow$  8.5Hz), 5.41 (1H, br s), 3.8 (3H, s), 3.70-3.35 (4H, br m), 3.35-3.15 (2H, m), 1.23 (6H, t,  $\downarrow$  7.2Hz); m/z (ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).



**EXAMPLE 60****(S)-3-[4-(Quinazolin-4-ylamino)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

5  $\delta_H$  ( $d_6$  DMSO, 390K) 8.62 (1H, s), 8.55 (1H, d,  $\downarrow$  8.8Hz), 7.90-7.82 (5H, m), 7.66-7.62 (1H, nr m), 7.34 (2H, d,  $\downarrow$  8.5Hz), 7.09 (1H, br s), 5.25 (1H, br s), 3.64-3.56 (4H, m), 3.35 (1H, dd,  $\downarrow$  14.2, 5.1Hz), 3.20 (1H, dd,  $\downarrow$  14.2, 9.1Hz), 1.23 (6H, t,  $\downarrow$  7.15Hz);  $m/z$  (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

**10 EXAMPLE 61****(S)-3-[4-[(6,7-Dimethoxyquinazolin-4-yl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

$\delta_H$  (CDCl<sub>3</sub>) 9.39 (1H, s), 8.41 (1H, s), 7.81 (1H, s), 7.67 (3H, dd,  $\downarrow$  8.5, 3.8Hz), 7.25 (2H, d,  $\downarrow$  8.4Hz), 7.16 (1H, s), 5.12 (1H, br s), 3.93 (3H, s),  
15 3.91 (3H, s), 3.60-3.40 (4H, m), 3.20-2.90 (2H, m), 1.09 (6H, t,  $\downarrow$  7.0Hz);  $m/z$  (ES<sup>+</sup>, 70V) 520 (MH<sup>+</sup>).

**EXAMPLE 62****(S)-3-[4-[(6,7-Dimethoxyquinazolin-4-yl)amino]phenyl]-2-[(2-n-propylamino)-3,4-dioxo-1-cyclobutenyl]amino]propanoic acid**

20  $\delta_H$  (DMSO) 9.40 (1H, s), 8.42 (1H, s), 7.81 (1H, s), 7.70 (1H, s), 7.66 (2H, d,  $\downarrow$  8.3Hz), 7.16 (2H, d,  $\downarrow$  7.9Hz), 7.15 (1H, s), 4.82 (1H, br s), 3.93 (3H, s), 3.91 (3H, s), 3.6-2.9 (4H, m), 1.49 (2H, dd,  $\downarrow$  14.1, 7.0Hz), 0.86 (3H, t,  $\downarrow$  7.3Hz);  $m/z$  (ES<sup>+</sup>, 70V) 506 (MH<sup>+</sup>).

25

**EXAMPLE 63****Methyl (S)-3-[4-(6-methoxyquinazolin-4-ylamino)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

$\delta_H$  (CDCl<sub>3</sub>) 8.65 (1H, s), 7.83 (1H, d,  $\downarrow$  9.1Hz), 7.69 (3H, s, d,  $\downarrow$  8.0Hz),  
30 7.45 (1H, dd,  $\downarrow$  9.2, 2.6Hz), 7.13 (2H, d,  $\downarrow$  8.5Hz), 5.40 (1H, br s), 3.95 (3H, s), 3.79 (3H, s), 3.6-3.41 (4H, br m), 3.48 (1H, dd,  $\downarrow$  14.1, 5.5Hz), 3.22 (1H, dd,  $\downarrow$  14.1, 7.0Hz), 1.29 (6H, t,  $\downarrow$  7.2Hz);  $m/z$  (ES<sup>+</sup>, 70V) 504 (MH<sup>+</sup>).

**EXAMPLE 64**

35 **(S)-3-[4-(6-Methoxyquinazolin-4-ylamino)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta_H$  ( $d_6$  DMSO, 370K); 9.35 (1H, br s), 8.40 (1H, s), 7.89 (1H, d,  $\downarrow$  2.7Hz, 7.54 (2H, d,  $\downarrow$  8.6Hz), 7.71 (1H, s), 7.49 (1H, d,  $\downarrow$  2.7Hz), 7.28 (2H, d,  $\downarrow$  8.5Hz), 7.15 (1H, br s), 5.14 (1H, br s), 3.97 (3H, s), 3.42-3.6 (4H, m), 3.28 (1H, dd,  $\downarrow$  14.1, 4.9Hz), 3.60-3.42 (4H, m), 3.28 (1H, dd,  $\downarrow$  14.1, 4.9Hz),  
5 3.14 (1H, dd,  $\downarrow$  14.1, 9.2Hz), 1.16 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  ( $ES^+$ , 70V) 490 ( $MH^+$ )

The compounds of Examples 65 to 68 were prepared from Intermediate 32 in a manner similar to that described for Examples 56 to 58.

10

**EXAMPLE 65**

Methyl 3-{4-[(6,7-dimethoxy-4-quinazolinyl)amino]-3-methoxyphenyl}-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate

15  $\delta_H$  (DMSO  $d_6$ , 390K) 8.54 (1H, br s), 8.38 (1H, s), 7.75 (1H, d,  $\downarrow$  7.8Hz), 7.66 (1H, s), 7.34 (1H, br d  $\downarrow$  8.5Hz), 7.25 (1H, br s), 7.20 (1H, s), 6.97 (1H, d,  $\downarrow$  1.9Hz), 6.85 (1H, br s), 5.15-5.09 (1H, m), 3.97 (3H, s), 3.96 (3H, s), 3.78 (3H, s), 3.76 (3H, s), 3.52-3.47 (2H, m), 3.26 (1H, dd,  $\downarrow$  14.1, 5.6Hz), 3.12 (1H, dd,  $\downarrow$  14.1, 8.0Hz), 1.59 (2H, sext,  $\downarrow$  7.2Hz), 0.93 (3H, t,  $\downarrow$   
20 7.4Hz);  $m/z$  ( $ES^+$  70V) 550 ( $MH^+$ ).

**EXAMPLE 66**

3-{4-[(6,7-Dimethoxy-4-quinazolinyl)amino]-3-methoxyphenyl}2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

25  $\delta_H$  (DMSO  $d_6$ , 390K) 8.38 (1H, s), 7.73 (1H, d,  $\downarrow$  8.0Hz), 7.66 (1H, s), 7.27 (1H, br s), 7.20 (1H, s), 6.99 (1H, d,  $\downarrow$  1.8Hz), 6.87 (1H, dd,  $\downarrow$  8.0, 1.9Hz), 5.02 (1H, m), 3.97 (3H, s), 3.96 (3H, s), 3.83 (3H, s), 3.49 (2H, q,  $\downarrow$  6.3Hz), 3.27 (1H, dd,  $\downarrow$  14.1, 5.4Hz), 3.11 (1H, dd,  $\downarrow$  14.1, 7.8Hz), 1.59 (2H, sext,  $\downarrow$  7.2Hz), 0.93 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  ( $ES^+$ , 70V) 536 ( $MH^+$ ).

30

**EXAMPLE 67**

Methyl 3-{4-[(6,7-dimethoxy-4-quinazolinyl)amino]-3-methoxyphenyl}-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate

$\delta_H$  (DMSO  $d_6$ , 390K) 8.33 (1H, br s), 8.15 (1H, s), 7.51 (1H, d,  $\downarrow$  8.1Hz),  
35 7.44 (1H, s), 6.98 (1H, s), 6.92 (1H, d,  $\downarrow$  9.0Hz), 6.82 (1H, d,  $\downarrow$  1.1Hz), 6.69 (1H, dd,  $\downarrow$  8.0, 1.9Hz), 5.15-5.09 (1H, m), 3.76 (3H, s), 3.75 (3H, s), 3.61

(3H, s), 3.55 (3H, s), 3.35 (4H, q,  $\downarrow$  7.1Hz), 3.11 (1H, dd,  $\downarrow$  14.2, 5.1Hz), 2.94 (1H, dd,  $\downarrow$  14.2, 9.5Hz), 0.96 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 564 (MH<sup>+</sup>).

5 **EXAMPLE 68**

**3-{4-[(6,7-Dimethoxy-4-quinazolinyl)amino]-3-methoxyphenyl}-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

$\delta$ H (DMSO d<sub>6</sub>, 390K), 8.49 (1H, s), 7.97 (1H, br s), 7.51-7.49 (1H, m), 7.38 (1H, s), 7.21 (1H, br d), 7.12 (1H, s), 6.96 (1H, dd,  $\downarrow$  7.9, 1.3Hz), 5.28-5.25 (1H, m), 4.00 (6H, s), 3.81 (3H, s), 3.58 (1H, q,  $\downarrow$  7.1Hz), 3.35 (1H, dd,  $\downarrow$  14.2, 4.8Hz), 3.20 (1H, dd,  $\downarrow$  14.2, 9.7Hz), 1.18 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 550 (MH<sup>+</sup>).

**EXAMPLE 69**

15 **Methyl (S)-3-{4-[(6,7-dimethoxy-4-quinazolinyl)amino]phenyl}-2-(2-tert butyl-3,4-dioxocyclobut-1-enylamino)propanoate**

A mixture of methyl-(S)-{4-[(6,7-dimethoxy-4-quinazolinyl)amino]phenyl}-2-amino propanoate (332mg, 0.869mmol) and Intermediate 4 (171mg, 0.87mmol) in MeOH (10ml) was heated at reflux for 5 days. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with dil. HCl, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (SiO<sub>2</sub>; MeOH/DCM, 7:93) gave the title compound as a brown glass (275mg).  $\delta$ H (DMSO d<sub>6</sub>) 9.39 (1H, s), 8.62 (1H, br d), 8.40 (1H, d,  $\downarrow$  1.2Hz), 7.81 (1H, s), 7.69-7.65 (2H, m), 7.22 (2H, d,  $\downarrow$  8.5Hz), 5.08 (1H, m), 3.94 (3H, s), 3.91 (3H, s), 3.74 (3H, s), 3.30 (1H, m), 3.02 (1H, dd,  $\downarrow$  13.5, 11.2Hz), 1.22 (9H, s);  $m/z$  (ES<sup>+</sup>, 70V) 519 (MH<sup>+</sup>).

**EXAMPLE 70**

30 **Ethyl-(S)-3-{4-[(3-chloro-6,7-dimethoxy-4-quinazolinyl)amino]phenyl}-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate**

Prepared in a similar manner to the compound of Example 56 from the Intermediate 45.  $\delta$ H (CD<sub>3</sub>OD) 7.73 (2H, d,  $\downarrow$  8.6Hz), 7.73 (1H, s), 7.27 (2H, d,  $\downarrow$  8.6Hz), 7.06 (1H, s), 5.28 (1H, m), 5.07 and 4.62 (1H, br), 4.23 (2H, q), 4.00 (3H, s), 3.97 (3H, s), 3.35 (1H, m), 3.05 (1H, m), 1.40 (6H, d,  $\downarrow$  6.2Hz), 1.30 (3H, t,  $\downarrow$  7.3Hz).

**EXAMPLE 71****Ethyl-(S)-3-(4-((3-chloro-6,7-dimethoxy-4-quinazolinyl)amino)phenyl)-2-((2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino)propanoate**

Prepared in a similar manner to the compound of the Example 57 from the compound of Example 70.  $\delta$ H (CD<sub>3</sub>OD) 7.72 (1H, s), 7.70 (2H, d,  $\downarrow$  8.6Hz), 7.29 (2H, d,  $\downarrow$  8.6Hz), 7.04 (1H, s), 5.33 (1H, dd), 4.25 (2H, q,  $\downarrow$  7.1Hz), 3.99 (3H, s), 3.96 (3H, s), 3.58 (4H, br), 3.44 (1H, dd), 3.10 (1H, dd), 1.30 (3H, t,  $\downarrow$  7.1Hz), 1.20 (6H, t,  $\downarrow$  7.2Hz).

**EXAMPLE 72****(S)-3-(4-((3-Chloro-6,7-dimethoxy-4-quinazolinyl)amino)phenyl)-2-((2-N,N-diethylamino-cyclobut-1-enyl)amino)propanoic acid**

Prepared in a similar manner to the compound of Example 58 from the compound of Example 71.  $\delta$ H (d<sub>6</sub> DMSO) 7.86 (1H, s), 7.65 (2H, d,  $\downarrow$  8.6Hz), 7.31 (2H, d,  $\downarrow$  8.6Hz), 7.16 (1H, s), 5.15 (1H, m), 3.97 (3H, s), 3.95 (3H, s), 3.53 (4H, m), 3.20 (1H, m), 3.13 (1H, m), 1.50 (6H, t,  $\downarrow$  7.1Hz).  $m/z$  (ES<sup>+</sup>) 554 (MH<sup>+</sup>).

**EXAMPLE 73****(S)-3-(4-((6,7-Dimethoxy-4-quinazolinyl)amino)phenyl)-2-(2-*t*-butyl-3,4-dioxocyclobut-1-enyl)amino)propanoic acid**

Prepared in a similar manner to the compound of Example 58 from the compound of Example 69.  $\delta$ H (DMSO d<sub>6</sub>, 370K) 8.40 (1H, s), 7.94 (1H, d,  $\downarrow$  9.2Hz), 7.83 (1H, s), 7.58 (2H, d,  $\downarrow$  8.5Hz), 7.17 (2H, d,  $\downarrow$  8.6Hz), 7.14 (1H, s), 4.96-4.90 (1H, m), 3.89 (3H, s), 3.87 (3H, s), 3.22 (1H, dd,  $\downarrow$  14.1, 4.5Hz), 3.04 (1H, dd,  $\downarrow$  14.0, 10.2Hz), 1.17 (9H, s).  $m/z$  (ES<sup>+</sup>, 70V) 505 (MH<sup>+</sup>).

**EXAMPLE 74****Ethyl-(S)-3-(4-((5-methyl-4-quinazolinyl)amino)phenyl)-2-((2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino)propanoate**

Intermediate 38 (800mg, 2.3mmol) and 3,4-diisopropoxy-3-cyclobuten-1,2-dione (453mg, 1 equiv) were stirred at RT in anhydrous MeOH (5m) for 17h. The solvent was removed *in vacuo* and the residue purified by column chromatography (silica, 75:25 EtOAc-isohexane) to give the title compound.  $\delta$ H (DMSO d<sub>6</sub>; 350K), 8.70 (broad signal), 8.50 (1H, s), 7.60

(4H, m), 7.30 (1H, d,  $\downarrow$  7.0Hz), 7.20 (2H, d,  $\downarrow$  8.4Hz), 5.20 (1H, m), 5.60 (1H, broad s), 4.20 (2H, m), 3.20 (1H, m), 3.10 (1H, m), 3.00 (3H, s), 1.30 (6H, d,  $\downarrow$  6.2Hz), 1.20 (3H, m);  $m/z$  (ES<sup>+</sup>, 70V) 489 (MH<sup>+</sup>).

5 **EXAMPLE 75**

**Ethyl (S)-3-(4-[(5-methyl-4-quinazolinyl)amino]phenyl)-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoate**

The compound of Example 74 (250mg, 0.5mmol) and N,N-diethylamine were stirred at RT in anhydrous (5ml) MeOH for 17h. The solvent was removed *in vacuo* and the residue purified by column chromatography (silica; EtOAc to 95% EtOAc : 5% MeOH ) to isolate the title compound (200mg) as an off-white solid.  $\delta$ H (DMSO d<sub>6</sub>), 8.60 (1H, s), 8.50 (1H, s), 7.80 (1H, d,  $\downarrow$  9.1Hz), 7.60 (4H, m), 7.40 (1H, d,  $\downarrow$  7.0Hz), 7.20 (2H, d,  $\downarrow$  6.8Hz), 5.20 (1H, m), 4.00 (1H, m), 3.70 (3H, s), 3.50 (4H, broad signal), 3.20 (1H, m), 3.00 (1H, m), 2.90 (3H, s), 1.20 (6H, m).  $m/z$  (ES<sup>+</sup>, 70V) 488 (MH<sup>+</sup>).

**EXAMPLE 76**

20 **(S)-3-(4-[(5-Methyl-4-quinazolinyl)amino]phenyl)-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid**

The compound of Example 75 (190mg, 0.38mmol) and lithium hydroxide monohydrate (19mg) were stirred in a solvent mixture of MeOH (3ml), THF (1.5ml), and water (1.5ml) for 17h. The solvent was removed *in vacuo* and the residue dissolved in water, the solution neutralised with HCl, concentrated *in vacuo* and the residue purified by column chromatography (silica; 200:20:3:2 DCM:MeOH:AcOH:H<sub>2</sub>O) to isolate the title compound as yellow solid.  $\delta$ H (DMSO d<sub>6</sub>, 350K), 8.50 (1H, broad signal), 7.70 (3H, broad signal), 7.40-7.20 (3H, m), 5.10 (1H, m), 3.6 (4H, m), 3.30 (1H, m), 3.10 (1H, m), 1.10 (6H, t,  $\downarrow$  7.2Hz),  $m/z$  (ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).

30

Also prepared in a similar manner to that described for Examples 75 and 76 from the compound of Example 74 were the compounds of Examples 77 and 78:

35 **EXAMPLE 77**

**Methyl (S)-3-(4-[(5-methyl-4-quinazolinyl)amino]phenyl)-2-[(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enyl)amino]propanoate**

5  $\delta$ H (DMSO  $d_6$ , 350K), 8.50 (1H, broad s), 7.80-7.60 (4H, m), 7.40 (1H, m), 7.30 (2H, m), 5.30 (1H, m), 3.70 (3H, s), 3.50 (4H, m), 3.40 (1H, m), 3.20 (1H, m), 3.10 (3H, s), 1.60 (4H, m), 0.90 (6H, t,  $\downarrow$  7.4Hz),  $m/z$  (ES<sup>+</sup>, 70V) 516 (MH<sup>+</sup>)

**EXAMPLE 78**

10 **(S)-3-(4-[(5-Methyl-4-quinazolinyl)amino]phenyl)-2-[(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid**

$\delta$ H (DMSO  $d_6$ , 350K), 8.70 (1H, s), 7.80 (2H, m), 7.70-7.40 (3H, m), 7.40 (2H, d,  $\downarrow$  8.5Hz), 5.20 (1H, m), 3.60 (4H, m), 3.40 (1H, m), 3.20 (1H, m), 3.00 (3H, s), 1.50 (4H, m), 0.90 (6H, t,  $\downarrow$  7.3Hz),  $m/z$  (ES<sup>+</sup>, 70V) 502 (MH<sup>+</sup>).

15

**EXAMPLE 79**

**Ethyl-(S)-3-(4-[(6-(trifluoromethoxy)-4-quinazolinyl)amino]phenyl)-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate**

20 Prepared in a similar manner to Example 74 from the compound of Intermediate 43.  $\delta$ H (DMSO  $d_6$ , 300K), 9.20-9.00 (1H, m), 8.70 (2H, m), 8.00 (2H, m), 7.80 (2H, m), 7.30 (2H, m), 5.20 (1H, m), 5.00 (1H, m), 4.50 and 4.20 (1H, 2, sets m), 3.80 (3H, m), 3.30 (1H, m), 3.00 (1H, m), 1.30 (6H, m),  $m/z$  (ES<sup>+</sup>, 70V) 545 (MH<sup>+</sup>).

25 **EXAMPLE 80**

**Methyl (S)-3-(4-[(6-(trifluoromethoxy)-4-quinazolinyl)amino]phenyl)-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoate**

30 Prepared from the compound of Example 79 in a similar manner to that described for Example 75.  $\delta$ H (CD<sub>3</sub>OD), 8.50 (1H, s), 8.40 (1H, s), 7.90 (1H, d,  $\downarrow$  9.1Hz), 7.80 (1H, m), 7.70 (2H, d,  $\downarrow$  8.6Hz), 7.30 (2H, d,  $\downarrow$  8.6Hz), 5.50 (1H, m), 3.80 (3H, s), 3.60 (4H, broad signal), 3.50 (1H, m), 3.10 (1H, m), 1.20 (6H, t,  $\downarrow$  7.2Hz),  $m/z$  (ES<sup>+</sup>, 70V) 544 (MH<sup>+</sup>).

**EXAMPLE 81**

35 **(S)-3-(4-[(6-(Trifluoromethoxy)-4-quinazolinyl)amino]phenyl)-2-[(2-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid**



Prepared from Example 80 in a similar manner to that described for Example 76.  $\delta$ H (DMSO, 340K), 9.80 (bd s), 8.60 (2H, m), 8.00-7.70 (4H, m), 7.30 (2H, d), 5.20 (1H, m), 3.50 (4H, m), 3.30 (1H, m), 3.10 (1H, m), 1.20 (6H, t,  $\downarrow$  7.1Hz)  $m/z$  (ES<sup>+</sup>, 70V) 544 (MH<sup>+</sup>).

5

**EXAMPLE 82**

**Methyl-(S)-3-(4-([6-(trifluoromethoxy)-4-quinazolinyl]amino)phenyl)-2-[(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enyl)amino]propanoate**

10 Prepared from the compound of Example 79 in a similar manner to that described for Example 75.  $\delta$ H (CD<sub>3</sub>OD), 8.50 (1H, s), 8.40 (1H, broad signal), 7.90 (1H, d,  $\downarrow$  9.2Hz), 7.85-7.70 (3H, m), 7.30 (1H, d,  $\downarrow$  8.5Hz), 5.40 (1H, m), 3.80 (3H, s), 3.60 (5H, broad signal), 3.10 (1H, m), 1.60 (4H, m), 0.90 (3H, t,  $\downarrow$  7.4Hz),  $m/z$  (ES<sup>+</sup>, 70V) 586 (MH<sup>+</sup>).

15

**EXAMPLE 83**

**(S)-3-(4-([6-(Trifluoromethoxy)-4-quinazolinyl]amino)phenyl)-2-[(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid**

20 Prepared from the compound of Example 82 in a similar manner to that described for Example 76.  $\delta$ H (DMSO d<sub>6</sub>, 350K), 9.70 (broad signal), 8.60 (2H, m), 7.90 (1H, d,  $\downarrow$  9.2Hz), 7.70 (3H, m), 7.30 (2H, d,  $\downarrow$  8.0Hz), 5.20 (1H, m), 3.50 (4H, m), 3.30 (1H, m), 3.200 (1H, m), 1.60 (4H, m), 0.90 (3H, t,  $\downarrow$  7.4Hz),  $m/z$  (ES<sup>+</sup>, 70V) 572 (MH<sup>+</sup>).

25 The compounds of Examples 84 to 89 were prepared in a similar manner to that described for the preparation of Intermediate 8 from N-BOC-L-tyrosine methyl ester and the appropriate quinazoline and then derivatised in a manner similar to that described for Examples 56 to 58.

**EXAMPLE 84**

**Methyl (S)-3-[4-(6,7-dimethoxyquinazolin-4-yloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

30  $\delta$ H (CDCl<sub>3</sub>) 8.57 (1H, s), 7.54 (1H, s), 7.33 (1H, s), 7.25-7.17 (5H, m), 5.55-4.9 (1H, m), 4.07 (6H, s), 3.83 (3H, s), 3.55-3.4 (5H, m), 3.31 (1H, dd,  $\downarrow$  9.0, 5.5Hz), 1.25 (6H, t,  $\downarrow$  7.2Hz),  $m/z$  (ES<sup>+</sup>, 70V) 535 (MH<sup>+</sup>).

35

**EXAMPLE 85**

**(S)-3-[4-[(6,7-Dimethoxyquinazolin-4-yl)oxy]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

5  $\delta_H$  ( $d_6$  DMSO, 370K) 8.58 (1H, s), 7.64 (1H, s), 7.44-7.40 (3H, m), 7.28 (2H, d,  $\downarrow$  8.5Hz), 5.23 (1H, br s), 4.06 (3H, s), 4.04 (3H, s), 3.66-3.56 (4H, m), 3.39 (1H, dd,  $\downarrow$  14.1, 4.6Hz), 3.21 (1H, dd,  $\downarrow$  14.1, 9.6Hz), 1.22 (6H, t,  $\downarrow$  7.1Hz),  $m/z$  (ES<sup>+</sup>, 70V) 521 (MH<sup>+</sup>),

**EXAMPLE 86**

10 **Methyl (S)-3-[4-(6-methoxyquinazolin-4-yloxy)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoate**

$\delta_H$  (CDCl<sub>3</sub>) 8.62 (1H, s), 7.95 (2H, d,  $\downarrow$  9.0Hz), 7.59-7.54 (2H, m), 7.26-7.18 (3H, m), 5.47-5.42 (1H, m), 5.30 (1H, d,  $\downarrow$  8.4Hz), 3.99 (3H, s), 3.83 (3H, s), 3.60-3.10 (6H, m), 1.67-1.60 (4H, m), 0.92 (6H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 533 (MH<sup>+</sup>).

**EXAMPLE 87**

**(S)-3-[4-(6-Methoxyquinazolin-4-yloxy)phenyl]-2-(2-N,N-di-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20 ( $d_6$  DMSO) 8.57 (1H, s), 7.92 (1H, d,  $\downarrow$  10.0Hz), 7.65 (2H, d,  $\downarrow$  7.3Hz), 7.37 (2H, d,  $\downarrow$  8.7Hz), 7.24 (2H, d,  $\downarrow$  8.6Hz), 7.09 (1H, br s), 5.13 (1H, br s), 3.98 (3H, s), 3.59-3.39 (4H, m), 3.35 (1H, dd,  $\downarrow$  14.5, 5.0Hz), 3.17 (1H, dd,  $\downarrow$  14.1, 9.4Hz), 1.67-1.50 (4H, m), 0.87 (6H, t,  $\downarrow$  7.3Hz);  $m/z$  (ES<sup>+</sup>, 70V) 519 (MH<sup>+</sup>)

25

**EXAMPLE 88**

**(S)-3-[4-(6-Methoxyquinazolin-4-yloxy)phenyl]-2-(2-n-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

30  $\delta_H$  ( $d_6$  DMSO, 370K) 8.59 (1H, s), 7.92 (1H, d,  $\downarrow$  9.8Hz), 7.65 (2H, d,  $\downarrow$  7.3Hz), 7.35-7.24 (5H, m), 4.97 (1H, br s), 3.99 (3H, s), 3.50 (2H, t,  $\downarrow$  6.3Hz), 3.29 (1H, dd,  $\downarrow$  14.0, 5.4Hz), 3.13 (1H, dd,  $\downarrow$  14.1, 7.4Hz), 1.58 (2H, dd,  $\downarrow$  14.2, 7.1Hz), 0.92 (3H, t,  $\downarrow$  7.4Hz);  $m/z$  (ES<sup>+</sup>, 70V) 477 (MH<sup>+</sup>).

**EXAMPLE 89**

35 **(S)-3-[4-(6-Methoxyquinazolin-4-yloxy)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**



$\delta_H$  (DMSO, 370K) 8.58 (1H, s), 7.92 (1H, d,  $\downarrow$  9.9Hz), 7.65 (2H, d,  $\downarrow$  4.7Hz), 7.39 (2H, d,  $\downarrow$  8.5Hz), 7.25 (2H, d,  $\downarrow$  8.8Hz), 5.21 (1H, br s), 3.98 (3H, s), 3.6-3.5 (4H, m), 3.34 (1H, dd,  $\downarrow$  14.2, 5.1Hz), 3.17 (1H, dd,  $\downarrow$  14.1, 9.9Hz), 1.17 (6H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 461 (MH<sup>+</sup>).

5

**EXAMPLE 90****(S)-Ethyl-3-[4-(isoquinolin-1-ylamino)phenyl]-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate**

A solution of Intermediate 10 (426mg, 1.27mmol) and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (301mg, 1.52mmol) in absolute ethanol (5.0ml) was stirred at 40° under N<sub>2</sub> for 18h. The volatiles were removed *in vacuo* and the residue chromatographed (SiO<sub>2</sub>; 25-50% EtOAc/hexane) to afford the title compound as a pale orange foam (585mg, 97%).  $\delta_H$  (CDCl<sub>3</sub>) 8.04 (1H, d,  $\downarrow$  5.8Hz), 7.98 (1H, d,  $\downarrow$  8.4Hz), 7.72 (1H, d,  $\downarrow$  7.8Hz), 7.62 (1H, obscured m), 7.61 (2H, d,  $\downarrow$  8.3Hz), 7.52 (1H, app.t,  $\downarrow$  7.0Hz), 7.35 (1H, br s), 7.12-7.08 (3H, m), 6.60, 6.03, 5.13 and 4.59 (together 1H, m), 5.32 (1H, m), 4.24 (2H, q,  $\downarrow$  7.1Hz), 3.25-3.01 (2H, br m), 1.39 (6H, d,  $\downarrow$  6.1Hz), 1.30 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).

20

**EXAMPLE 91****Ethyl (S)-3-[4-(isoquinolin-1-ylamino)phenyl]-2-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoate**

A solution of the compound of Example 90 (585mg, 1.24mmol) and diethylamine (181mg, 225 $\mu$ l, 2.48mmol) in absolute ethanol (2ml) was heated at 50° under N<sub>2</sub> for 18h. The volatiles were removed *in vacuo* affording the title compound as a dull orange foam (520mg).  $\delta_H$  (CDCl<sub>3</sub>) 8.05 (1H, d,  $\downarrow$  5.8Hz), 7.96 (1H, d,  $\downarrow$  8.3Hz), 7.75 (1H, d,  $\downarrow$  7.6Hz), 7.65 (1H, m), 7.63 (2H, d,  $\downarrow$  8.5Hz), 7.55 (1H, app.t,  $\downarrow$  7.0Hz), 7.23 (1H, br s), 7.11 (1H, m), 7.10 (2H, d,  $\downarrow$  8.5Hz), 5.39 (1H, narrow m), 4.25 (2H, q,  $\downarrow$  7.1Hz), 3.65-3.35 (4H, br m), 1.32 (3H, t,  $\downarrow$  7.1Hz), 1.22 (6H, t,  $\downarrow$  7.2Hz);  $m/z$  (ES<sup>+</sup>, 70V) 487 (MH<sup>+</sup>).

30

**EXAMPLE 92****(S)-3-[4-(isoquinolin-1-ylamino)phenyl]-2-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

35

A solution of Example 91 (510mg, 1.05mmol) and LiOH.H<sub>2</sub>O (53mg, 1.26mmol) in water (8ml) and dioxan (8ml) was stirred at room temperature for 1.5h. Several drops of AcOH were added and the volatiles were removed *in vacuo*. The residue was chromatographed [silica, DCM (200-120), MeOH (20), AcOH (3), H<sub>2</sub>O(2)]. Freeze-drying from aqueous MeOH afforded the title compound as a pale yellow amorphous solid (230mg, 48%).  $\delta$ H (d<sup>6</sup> DMSO) 9.07 (1H, br s), 8.49 (1H, d,  $\downarrow$  8.3Hz), 7.95 (1H, d,  $\downarrow$  5.7Hz), 7.79-7.75 (3H, m's), 7.70-7.64 (2H, m's), 7.58 (1H, td,  $\downarrow$  8.3, 1.3Hz), 7.20 (2H, d,  $\downarrow$  8.4Hz), 7.13 (1H, d,  $\downarrow$  5.6Hz), 5.11 (1H, m), 3.65-3.38 (4H, br m), 3.22 (1H, dd,  $\downarrow$  13.9, 4.0Hz), 2.99 (1H, dd,  $\downarrow$  13.9, 11.0Hz) and 1.09 (6H, t,  $\downarrow$  7.0Hz);  $m/z$  (ES<sup>+</sup>, 70V) 459 (MH<sup>+</sup>).

### EXAMPLE 93

#### Ethyl (3S)-3-{4-[(tert-Butoxycarbonyl)amino]phenyl}-3-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate

Intermediate 12 (190mg, 0.62mmol) in MeOH was treated with 3,4-diisopropoxy-3-cyclobutene-1,2-dione (122mg) and N-methyl-morpholine (0.1ml) and stirred at RT for 16h. The solvent was removed and the product purified by column chromatography (SiO<sub>2</sub>;CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to give the title compound (176mg, 64%) as a white foamy solid.  $\delta$ H (DMSO) 7.41 (2H, d,  $\downarrow$  8.6Hz), 7.24 (2H, d,  $\downarrow$  8.6Hz), 5.29 (1H, m), 5.25 (1H, septet,  $\downarrow$  6.2Hz), 4.06 (2H, q,  $\downarrow$  7.1Hz), 2.99 (1H, dd,  $\downarrow$  15.8, 8.8Hz), 2.86 (1H, dd,  $\downarrow$  15.8, 6.0Hz), 1.40 (3H, d,  $\downarrow$  6.2Hz), 1.36 (3H, d,  $\downarrow$  6.2Hz), 1.16 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ESI, 70V) 469 (MNa<sup>+</sup>).

### EXAMPLE 94

#### Ethyl (3S)-3-(4-aminophenyl)-3-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate

The compound of Example 93 (176mg, 0.39mmol) was dissolved in EtOAc (10ml) and HCl gas was bubbled through. The reaction mixture was stirred for 2h and the solvent removed to give the title compound (130mg, 0.34mmol, 87%) as an oil.  $\delta$ H (DMSO 360K) 7.38 (2H, d,  $\downarrow$  8.5Hz), 7.21 (2H, d,  $\downarrow$  8.5Hz), 5.30 (1H, br m), 5.25 (1H, septet,  $\downarrow$  6.2Hz), 4.08 (2H, q,  $\downarrow$  7.1Hz), 2.99 (1H, dd,  $\downarrow$  15.8, 8.8Hz), 2.85 (1H, dd,  $\downarrow$  15.8, 6.0Hz), 1.40 (3H, d,  $\downarrow$  6.2Hz), 1.36 (3H, d,  $\downarrow$  6.2Hz), 1.15 (3H, t,  $\downarrow$  7.1Hz).

**EXAMPLE 95****Ethyl (3S)-3-{4-(3,5-dichloro-4-pyridylcarboxamido)phenyl}-3-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate**

The compound of Example 94 (max 2mmol) was dissolved in DCM (5ml) and N-methylmorpholine (1 equiv) and cooled to 0°. 3,5-dichloroisonicotinoyl chloride (463mg) was added and the reaction mixture stirred at RT for 16h then quenched with sodium bicarbonate solution. The organic layer was washed with dilute hydrochloric acid, water, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed. The product was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to give the title compound (636mg, 61%) as an oil.  $\delta$ H (DMSO, 390K) 10.47 (1H, br s), 8.69 (2H, s), 7.62 (2H, d,  $\downarrow$  8.4Hz), 7.39 (2H, d,  $\downarrow$  8.4Hz), 5.38 (1H, m), 5.25 (1H, septet,  $\downarrow$  6.1Hz), 4.10 (2H, q,  $\downarrow$  7.1Hz), 3.05 (1H, dd,  $\downarrow$  15.8, 8.6Hz), 1.42 (3H, d,  $\downarrow$  6.1Hz), 1.38 (3H, d,  $\downarrow$  6.1Hz), 1.18 (3H, t,  $\downarrow$  7.1Hz);  $m/z$  (ES<sup>+</sup>, 70V) 522 (MH<sup>+</sup>).

**EXAMPLE 96****Ethyl (3S)-3-{4-(3,5-dichloropyrid-4-ylcarboxamido)phenyl}-3-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoate**

The compound of Example 95 (318mg, 0.61mmol) was dissolved in MeOH (5ml) and diethylamine (0.13ml). The solution was stirred for 16h to give a white precipitate which was isolated by filtration and dried to give the title compound (247mg, 78%) as a white solid.  $\delta$ H (DMSO, 370K) 10.93 (1H, br s), 8.78 (2H, s), 7.61 (2H, d,  $\downarrow$  9.0Hz), 7.41 (2H, d,  $\downarrow$  9.0Hz), 5.83 (1H, m), 3.59 (3H, s), 3.53 (4H, br m), 3.08 (1H, dd,  $\downarrow$  16.0, 9.0Hz), 2.95 (1H, dd,  $\downarrow$  16.0, 6.0Hz), 1.10 (6H, t,  $\downarrow$  6.0Hz);  $m/z$  (ES<sup>+</sup>, 70V) 521 (MH<sup>+</sup>).

**EXAMPLE 97****(3S)-3-{4-(3,5-Dichloropyrid-4-yl-carboxamido)phenyl}-3-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl)amino]propanoic acid**

The compound of Example 96 (235mg, 0.45mmol) was dissolved in THF (5ml) and water (5ml) and lithium hydroxide (21mg) added. The solution was stirred at RT for 3h and the solvent removed *in vacuo*. The residue was dissolved in water (10ml) and acidified to pH 2 with dil. HCl to give a white precipitate (198mg, 0.39mmol, 87%) which was filtered and dried to afford the title compound.  $\delta$ H (DMSO, 390K) 10.43 (1H, br s), 8.69 (2H, s),

- 7.60 (2H, d,  $\downarrow$  8.5Hz), 7.45 (2H, d,  $\downarrow$  8.5Hz), 7.29 (1H, br s), 5.82 (1H, m, ), 3.60 (2H, q,  $\downarrow$  7.0Hz), 3.58 (2H, q,  $\downarrow$  7.0Hz), 3.02 (1H, dd,  $\downarrow$  15.8, 8.2Hz, ), 2.90 (1H, dd,  $\downarrow$  15.8, 6.1Hz), 1.20 (6H, t,  $\downarrow$  7.0Hz); ;  $m/z$  (ES<sup>+</sup>, 70V) 507 (MH<sup>+</sup>). Analysis by chiral HPLC on Chirobiotic T column eluting with
- 5 MeOH/0.6%HOAc gave single peak eluting at 5.58 minutes.

#### EXAMPLE 98

##### (3R)-3-{4-(3,5-Dichloropyrid-4-ylcarboxamido)phenyl-3-[(2-N,N-diethylamino)-3,4-dioxo-1-cyclobutenyl]amino}propanoic acid

- 10 This was prepared by the same route as the (S)-enantiomer Example 97 using the appropriate chiral amine. Analysis by chiral HPLC on Chirobiotic T column eluting with MeOH/0.6%HOAc gave single peak eluting at 6.54 minutes.

#### 15 EXAMPLE 99

##### Methyl (3R)-3-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]-3-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}propanoate

- Intermediate 16 (580mg, 1.38mmol) was dissolved in MeOH (6ml) and DIPEA (0.53ml) and 3,4-diisopropoxy-3-cyclobuten-1,2-dione (300mg)
- 20 added. The solution was stirred for 16h and the solvent removed. The residue was purified by column chromatography (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1) to give the title compound (539mg, 75%) as a yellow oil.  $\delta$ H (DMSO, 350K) 8.99 (1H, br m), 8.54 (1H, s), 7.57 (1H, s), 7.49 (2H, d,  $\downarrow$  8.6Hz), 7.38 (1H, s), 7.32 (2H, d,  $\downarrow$  8.6Hz), 5.40 (1H, m), 5.27 (1H, septet,  $\downarrow$
- 25 6.2Hz), 4.01 (3H, s), 3.98 (3H, s), 3.64 (3H, s), 3.10 (1H, dd,  $\downarrow$  16.1, 5.8Hz), 2.97 (1H, dd,  $\downarrow$  16.1, 5.8Hz), 1.42 (3H, d,  $\downarrow$  6.2Hz), 1.38 (3H, d,  $\downarrow$  6.2Hz), ;  $m/z$  (ES<sup>+</sup>, 70V) 522 (MH<sup>+</sup>).

#### EXAMPLE 100

- 30 Methyl (3R)-3-[(2-N,N-diethylamino-3,4-dioxo-1-cyclobutenyl]amino)-3-{4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl}propanoate

- The compound of Example 99 (265mg, 0.51mmol) was dissolved in MeOH (3ml) and diethylamine added (0.1ml). The solution was stirred for 16h giving a white precipitate. The precipitate was filtered and dried to give the
- 35 title compound (177mg, 65%) as a white solid.  $\delta$ H (DMSO, 370K) 8.55 (1H, s), 7.59 (1H, s), 7.54 (2H, d,  $\downarrow$  8.5Hz), 7.32 (1H, s), 7.30 (2H, d,  $\downarrow$

8.5Hz, 5.94 (1H, m), 4.02 (3H, s), 3.99 (3H, s), 3.64 (3H, s), 3.60 (4H, septet,  $\downarrow$  7.1Hz), 3.15 (1H, dd,  $\downarrow$  15.7, 8.9Hz), 3.03 (1H, dd, J 15.7, 5.9Hz), 1.19 (6H, t,  $\downarrow$  7.1Hz), ;  $m/z$  (ES<sup>+</sup>, 70V) 535 (MH<sup>+</sup>).

5 **EXAMPLE 101**

**(R)-3-[(2-N,N-Diethylamino-3,4-dioxo-1-cyclobutenyl)amino]-3-[4-[(6,7-dimethoxy-4-quinazolinyl)oxy]phenyl]propanoic acid**

The compound of Example 100 (170mg, 0.32 mmol) was dissolved in THF (2ml) and water (2ml) and lithium hydroxide (20mg) was added. The solution was stirred at RT for 3h and the solvent removed. The residue was dissolved in water (10ml) and acidified to pH2 with dil. HCl to give a white precipitate (42mg, 25%) which was filtered and dried.  $\delta$ H (DMSO, 400K) 8.56 (1H, s), 7.60 (1H, s), 7.54 (2H, d,  $\downarrow$  8.6Hz), 7.39 (1H, s), 7.31 (2H, d,  $\downarrow$  8.6Hz), 5.90 (1H, m), 4.03 (3H, s), 3.99 (3H, s), 3.62 (2H, q,  $\downarrow$  7.1Hz), 3.60 (2H, q,  $\downarrow$  7.1Hz), 3.06 (1H, dd,  $\downarrow$  15.8, 8.2Hz), 2.95 (1H, dd,  $\downarrow$  15.8, 6.1Hz), 1.21 (3H, t,  $\downarrow$  7.1Hz), ;  $m/z$  (ES<sup>+</sup>70V) 521 (MH<sup>+</sup>).

**EXAMPLE 102**

20 **Ethyl (R)-3-[(2-isopropoxy-3,4-dioxo-1-cyclobutenyl)amino]-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propanoate**

Intermediate 23 (178mg, 0.53mmol) was dissolved in MeOH (5ml) and DIPEA (0.2ml), treated with 3,4-diisopropoxy-3-cyclobuten-1,2-dione (126mg) and stirred at RT for 16h. The solution was concentrated, dissolved in DCM (20ml), washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 50:1) to give the title compound (150mg, 60%) as an oil. (H (DMSO, 370K) 9.21 (1H, s), 9.09 (1H, br s), 8.70 (1H, br m), 8.65 (1H, d,  $\downarrow$  5.9), 8.33 (1H, d,  $\downarrow$  5.9Hz), 8.16 (1H, d,  $\downarrow$  5.7Hz), 7.87 (2H, d,  $\downarrow$  8.5Hz), 7.35 (2H, d,  $\downarrow$  8.5Hz), 7.28 (1H, d,  $\downarrow$  5.7Hz), 5.37 (1H, m), 5.27 (1H, septet,  $\downarrow$  6.2Hz), 4.10 (2H, qd,  $\downarrow$  7.1, 0.4Hz), 3.05 (1H, dd,  $\downarrow$  15.8, 8.9Hz), 2.93 (1H, dd,  $\downarrow$  15.8, 5.9), 1.43 (3H, d,  $\downarrow$  6.2Hz), 1.39 (3H, d,  $\downarrow$  6.2Hz), 1.18 (3H, t,  $\downarrow$  7.1Hz), ;  $m/z$  (ES<sup>+</sup>, 70V) 475 (MH<sup>+</sup>).

**EXAMPLE 103**

35 **Methyl (3R)-3-[(2-N,N-Diethylamino-3,4-dioxo-1-cyclobutenyl)amino]-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propanoate**

The compound of Example 102 (145mg, 0.3 mmol) in MeOH (2ml) was treated with diethylamine (0.07ml) and stirred at RT for 16h. The solvent was removed and the residue was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:1) to give the title compound (140mg, 98%) as a yellow oil.  $\delta$ H (DMSO, 370K) 9.21 (1H, s), 9.08 (1H, br s), 8.65 (1H, d,  $\downarrow$  5.9Hz), 8.33 (1H, d,  $\downarrow$  5.9Hz), 8.16 (1H, d,  $\downarrow$  5.7Hz), 7.86 (2H, d,  $\downarrow$  8.5Hz), 7.40 (2H, d,  $\downarrow$  8.5Hz), 7.27 (1H, d,  $\downarrow$  5.7Hz), 5.87 (1H, m), 3.63 (3H, s), 3.59 (2H, q,  $\downarrow$  7.1Hz), 3.57 (2H, q,  $\downarrow$  7.1Hz), 3.12 (1H, dd,  $\downarrow$  15.6, 8.8Hz), 2.99 (1H, dd,  $\downarrow$  15.6, 6.0Hz), 1.21 (3H, t,  $\downarrow$  7.1Hz), 1.18 (3H, t,  $\downarrow$  7.1Hz), ;  $m/z$  (ES<sup>+</sup>, 70V) 474 (MH<sup>+</sup>).

#### **EXAMPLE 104**

##### **(3R)-3-[(2-N,N-Diethylamino-3,4-dioxo-1-cyclobutenyl)amino-3-[4-(2,6-naphthyridin-1-ylamino)phenyl]propanoic acid**

The compound of Example 103 (140mg, 0.29mmol) was dissolved in THF (1ml) and water (1ml) and treated with lithium hydroxide (18mg). The solution was stirred at RT for 90 mins and concentrated *in vacuo*. The residue was dissolved in water and slowly acidified to pH4.5 with dilute HCl acid to give a yellow precipitate which was filtered and dried to give the title compound (60mg).  $\delta$ H (DMSO, 350K) 9.22 (1H, d,  $\downarrow$  0.8Hz), 8.66 (1H, d,  $\downarrow$  5.8Hz), 8.36 (1H, dd,  $\downarrow$  5.9, 0.8Hz), 8.15 (1H, d,  $\downarrow$  5.8Hz), 7.84 (2H, d,  $\downarrow$  8.5Hz), 7.40 (2H, d,  $\downarrow$  8.5Hz), 7.29 (1H, d,  $\downarrow$  5.8Hz), 5.83 (1H, m), 3.59 (2H, q,  $\downarrow$  7.1Hz), 3.57 (2H, q,  $\downarrow$  7.1Hz), 3.02 (1H, dd,  $\downarrow$  15.7, 8.8Hz), 2.90 (1H, dd,  $\downarrow$  15.7, 5.9Hz), 1.18 (6H, t,  $\downarrow$  7.1Hz),  $m/z$  (ES<sup>+</sup>, 70V) 460 (MH<sup>+</sup>).

The following derivatised resins were prepared to enable the preparation of compounds of the invention by solid phase synthesis:

##### **30 Resin bound (S)-3-(4-Aminophenyl)-2-(9-fluorenylmethoxy-carbonylamino)propanoic acid (1)**

Paramax Wang resin (Advanced Chemtech, 10g, 1.0mmol/g, 10mmol equivalent) in DMF (150ml) was treated with N- $\alpha$ -Fmoc-4-nitro-L-phenylalanine (22g, 50mmol), 2,6-dichlorobenzoyl chloride (7.0ml, 50mmol) and pyridine (4.0ml, 50mmol) and the mixture agitated under nitrogen at RT for 24h. The resin was filtered and washed with DMF and DCM then



unreacted resin sites were capped with 20% acetic anhydride in DMF for 30mins at RT. The resin was filtered and washed as before then treated with a 1M solution of stannous chloride dihydrate in DMF (100ml) at RT for 12h and washed with DMF and DCM to give the derivatised resin (1).

5

**Resin bound (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-aminopropanoic acid (2)**

Derivatised resin (1) from the above procedure was swollen in DCM (50ml) then treated with DIPEA (5.1ml, 29mmol) and 3,5-dichloropyridine-4-carbonylchloride (6.2ml, 29mmol) and agitated under nitrogen at RT for 12h. The resin was washed as before then treated with a 20% solution of piperidine in DMF (100ml) for 30mins at RT followed by thorough washing with DMC and DCM to give the derivatised resin (2).

15 **Resin bound (S)-3-[4-(3,5-dichloro-4-pyridylcarboxamido)phenyl]-2-(2-methoxy-3,4-dioxocyclobut-1-enylamino)propanoic acid (3)**

Derivatised resin (2) from the above procedure in DMF (100ml) was treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (4.1g, 29mmol) for 12h at 70° then filtered and washed with DMF and DCM to give the derivatised resin (3).

20 **Resin bound (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-methoxy-3,4-dioxocyclobut-1-enylamino)propanoic acid (4)**

Derivatised resin (4) was prepared in a similar manner to derivatised resin (3) from (RS)-3-(9-fluorenylmethoxycarbonylamino)-3-(4-nitrophenyl)propanoic acid. The latter was prepared as follows: A cold (0°) solution of (RS)-3-Amino-3-(4-nitrophenyl)propanoic acid [D. M. Kalvin and R. W. Woodward, J. Org. Chem. (1985) 50, 2259] (3.2g, 15mmol) in 10% aqueous sodium carbonate (60ml) and 1,4-dioxane (30ml) was treated portion-wise with 9-fluorenylmethoxycarbonyl-N-hydroxysuccinimide (5.6g, 17mmol) in 1,4-dioxane (15ml) and the mixture stirred at RT for 12h. The mixture was poured into water (300ml) and the aqueous phase washed 3 times with Et<sub>2</sub>O. The aqueous layer was then acidified with solid citric acid and extracted into Et<sub>2</sub>O. The combined organic layers were dried (MgSO<sub>4</sub>) and evaporated to a yellow oil then triturated from hexane and

35

EtOAc to afford (RS)-3-(9-fluorenylmethoxy-carbonylamino)-3-(4-nitrophenyl)propanoic acid as a yellow solid (1.8g);  $m/z$  (ES<sup>+</sup>, 70V) 432.

**Resin bound (S)-3-(4-Aminophenyl)-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino) propanoic acid (5)**

5 Paramax Wang resin (Advanced Chemtech, 10g, 1.0mmol/g, 10mmol equivalent) in DMF (150ml) was treated with N- $\alpha$ -Fmoc-4-nitro-L-phenylalanine (22g, 50mmol), 2,6-dichlorobenzoyl chloride (7.0ml, 50mmol) and pyridine (4.0ml, 50mmol) and the mixture agitated under  
10 nitrogen at RT for 24h. The resin was filtered and washed with DMF and DCM then unreacted resin sites were capped with 20% acetic anhydride in DMF for 30mins at RT. The resin was filtered and washed as before. A portion (4g) was treated with a 20% solution of piperidine in DMF (100ml) for 30mins at RT then filtered and washed with DMF and DCM. The resin  
15 was treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (1.9g, 13.4mmol) in DMF (50ml) for 12h at 70°C then filtered and washed with DMF and DCM. The resin was swollen in DCM (10ml) and EtOH (40ml) and treated with propylamine (1.6ml, 19.2mmol). The solution was agitated for 12h at RT then filtered and washed thoroughly with DCM. The resin was treated  
20 with a 1M solution of stannous chloride dihydrate in DMF (50ml) at RT for 8h then washed with DMF and DCM to give derivatised resin (5).

**Resin bound diethylphosphono- $\alpha$ -diazoacetate (6)**

25 Wang resin (Advanced Chem tech, 1.0g, 0.7mmol/g, 0.7mmol equivalent) was treated with diethyl-phosphonoacetate (0.68g, 3.5mmol), N,N'-diisopropylcarbodiimide 0.55ml, 3.5mmol) and 4-N,N-dimethylamino-pyridine (0.09g, 0.7mmol), in DCM (5.0ml). The mixture was agitated at ambient temperature for 16h. The resin was filtered and washed with DMF, MeOH and DCM. The resulting resin (1.0g) was treated with 4-acetamidobenzenesulfonyl azide (0.43g, 1.86mmol) and diazabicyclo-undec-7-ene (0.09g, 0.62mmol) in acetonitrile at ambient temperature for 16h. The  
30 resin was washed with DMF, MeOH and DCM to give derivatised resin (6) [FTIR (ATR)  $\nu_{\max}$  2132cm<sup>-1</sup>].

35 **Resin bound (S)-3-[4-(1-isoquinolylamino)phenyl]-2-(9-fluorenylmethoxycarbonylamino)propanoic acid (7)**



Wang resin (Advanced Chemtech, 3.0g, 0.7mmol/g, 2.1mmol equivalent) in DMF (50ml) was treated with (S)-3-[4-(1-isoquinolylamino)phenyl]-2-(9-fluorenylmethoxycarbonylamino)propanoic acid (3.3g, 6.3mmol), 2,6-dichlorobenzoyl chloride (1.5ml, 10.5mmol) and pyridine (0.8ml, 10.5mmol) and the mixture agitated under nitrogen at RT for 24h. The resin was filtered and washed with DMF and DCM then unreacted resin sites were capped with 20% acetic anhydride in DMF for 30mins at RT. The resin was filtered and washed as before to give derivatised resin (7).

10 **Resin bound (S)-3-[4-(1-isoquinolylamino)phenyl]-2-(2-methoxy-3,4-dioxocyclobut-1-enylamino)propanoic acid (8)**

Derivatised resin (7) from the above procedure was treated with a 20% solution of piperidine in DMF (100ml) for 30mins at RT followed by thorough washing with DMF and DCM. The resin was treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (4.7g, 33mmol) for 12h at 70° in DMF (50ml) then filtered and washed as before to give derivatised resin (8).

**Resin bound (S)-3-(4-benzoylphenyl)-2-(2-methoxy-3,4-dioxocyclobut-1-enyl)aminopropanoic acid (9)**

20 N- $\alpha$ -Fmoc-L-benzoylphenylalanine Wang resin (Advanced Chemtech, 400mg, 0.5mmol/g, 0.2mmol equivalent) was treated with a 20% solution of piperidine in DMF (5ml) for 30mins at RT then filtered and washed thoroughly with DMF and DCM. The resin was treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (200mg, 1.4mmol) for 12h at 70° in DMF (5ml) then filtered and washed as before to give derivatised resin (9).

**HPLC-MS**

HPLC-MS was performed on a Hewlett Packard 1100/MSD ES Single Quadropole system with diode array detector using either:

- 30 **Conditions A:** A Luna C18(2) 50 x 4.6mm (3 $\mu$ m particle size) column, running a gradient of 95% [20mM ammonium formate, pH 3.5], 5% [0.1% formic acid in acetonitrile] to 10% [20mM ammonium formate, pH 3.5], 90% [0.1% formic acid in acetonitrile] over 3min, then maintaining the mobile phase at that ratio for a further 2min. Flow rate 0.8ml/min.; or
- 35 **Conditions B:** A Luna C18(2) 50 x 2.0mm (3 $\mu$ m) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in

acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min.

MS was acquired by API electrospray in positive ion mode, at 70V,  
5 scanning from 150 to 750amu.

#### **EXAMPLE 105**

##### **(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclohexylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

10 To the derivatised resin (3), (120mg) was added DCM (0.2ml), EtOH (0.8ml) and a 1M solution of cyclohexylamine in DCM (0.5ml). The solution was agitated for 12h at RT followed by filtration and multiple washes with DCM. The resin was treated with 60% trifluoroacetic acid in DCM (1.5ml) for 3h with agitation and then filtered. The filtrate was  
15 evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (5mg).  
HPLC-MS (Conditions A) Retention time 3.5min MH<sup>+</sup> 531.

The following compounds of Examples 106 to 179 and 183 to 195 were  
20 prepared in a similar manner to the compound of Example 105, each using the starting material shown. For examples where the amine was added as a salt, 1 mol equivalent of DIPEA was also added.

#### **EXAMPLE 106**

##### **(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-adamantylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

1-Adamantylamine gave the title compound (4mg)  
HPLC-MS (Conditions A) Retention time 3.9min MH<sup>+</sup> 583

#### **EXAMPLE 107**

##### **(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-methoxyethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

2-Methoxyethylamine gave the title compound (10mg)  
HPLC-MS (Conditions A) Retention time 3.1min MH<sup>+</sup> 507

35

#### **EXAMPLE 108**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-methoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3-Methoxypropylamine gave the title compound (9mg)

HPLC-MS (Conditions A) Retention time 3.2min MH<sup>+</sup> 521

5

**EXAMPLE 109**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-thienylmethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

2-(Aminomethyl)thiophene gave the title compound (4mg)

10 HPLC-MS (Conditions A) Retention time 3.4min MH<sup>+</sup> 545

**EXAMPLE 110**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-morpholinoethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15

N-(2-Aminoethyl)morpholine gave the title compound (8mg)

HPLC-MS (Conditions A) Retention time 2.9min MH<sup>+</sup> 562

**EXAMPLE 111**

20

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3,4,5-trimethoxybenzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3,4,5-Trimethoxybenzylamine gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 3.4min MH<sup>+</sup> 629

25

**EXAMPLE 112**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-piperidinoethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

1-(2-Aminoethyl)piperidine gave the title compound (11mg)

30 HPLC-MS (Conditions A) Retention time 2.9min MH<sup>+</sup> 560

**EXAMPLE 113**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-(2-oxopyrrolidin-1-yl)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

35

1-(3-Aminopropyl)-2-pyrrolidinone gave the title compound (12mg)

HPLC-MS (Conditions A) Retention time 3.1min MH<sup>+</sup> 574

**EXAMPLE 114**

5 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-phenylpropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
3-Phenylpropylamine gave the title compound (8mg)  
HPLC-MS (Conditions A) Retention time 3.7min MH<sup>+</sup> 567

**EXAMPLE 115**

10 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-(1-imidazolyl)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
N-(3-Aminopropyl)imidazole gave the title compound (9mg)  
HPLC-MS (Conditions A) Retention time 2.8min MH<sup>+</sup> 557

**EXAMPLE 116**

15 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-piperonylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid  
Piperonylamine gave the title compound (3mg)  
20 HPLC-MS (Conditions A) Retention time 3.5min MH<sup>+</sup> 583

**EXAMPLE 117**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-benzyl-4-piperidinylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
25 4-Amino-1-benzylpiperidine gave the title compound (12mg)  
HPLC-MS (Conditions A) Retention time 3.1min MH<sup>+</sup> 622

**EXAMPLE 118**

30 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-pyridylmethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
2-(Aminomethyl)pyridine gave the title compound (14mg)  
HPLC-MS (Conditions A) Retention time 3.2min MH<sup>+</sup> 540

**EXAMPLE 119**

35 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclopentylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Cyclopentylamine gave the title compound (8mg)  
HPLC-MS (Conditions A) Retention time 3.4min MH<sup>+</sup> 517

**EXAMPLE 120**

5 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-phenylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

4-Phenylbutylamine gave the title compound (4mg)  
HPLC-MS (Conditions A) Retention time 3.8min MH<sup>+</sup> 581

10 **EXAMPLE 121**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-pyridylmethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

3-(Aminomethyl)pyridine gave the title compound (7mg)  
HPLC-MS (Conditions A) Retention time 3.0min MH<sup>+</sup> 540

15

**EXAMPLE 122**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3,3-dimethylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

3,3-Dimethylbutylamine gave the title compound (7mg)

20 HPLC-MS (Conditions A) Retention time 3.6min MH<sup>+</sup> 533

**EXAMPLE 123**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3,4-dichlorobenzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

25 3,4-Dichlorobenzylamine gave the title compound (11mg)  
HPLC-MS (Conditions A) Retention time 3.8min MH<sup>+</sup> 607

**EXAMPLE 124**

30 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-(1-piperazinyl)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

N-(2-aminoethyl)piperazine gave the title compound (5mg)  
HPLC-MS (Conditions A) Retention time 2.8min MH<sup>+</sup> 561

35 **EXAMPLE 125**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-pyrrolidinyl)ethylamino]-3,4-dioxocyclobut-1-enylamino]propanoic acid**

1-(2-aminoethyl)pyrrolidine gave the title compound (9mg)

5 HPLC-MS (Conditions A) Retention time 2.9min MH<sup>+</sup> 546

**EXAMPLE 126**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-hydroxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 3-Hydroxypropylamine gave the title compound (4mg)

HPLC-MS (Conditions A) Retention time 3.0min MH<sup>+</sup> 507

**EXAMPLE 127**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-cyclohexylanilino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15 4-Cyclohexylaniline gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 4.3min MH<sup>+</sup> 607

**EXAMPLE 128**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-morpholinoanilino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

20 4-Morpholinoaniline gave the title compound (5mg)

HPLC-MS (Conditions A) Retention time 3.4min MH<sup>+</sup> 610

**EXAMPLE 129**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-isopropylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Isopropylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 491

30

**EXAMPLE 130**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-tert-butylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Tert-butylamine gave the title compound (1mg)

35 HPLC-MS (Conditions B) Retention time 2.39min MH<sup>+</sup> 505



**EXAMPLE 131**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Propylamine gave the title compound (5mg)

5 HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 491

**EXAMPLE 132**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-benzylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

10 Benzylamine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.43min MH<sup>+</sup> 539

**EXAMPLE 133**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-(dimethylamino)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15

3-(Dimethylamino)propylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 1.92min MH<sup>+</sup> 534

20 **EXAMPLE 134**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-isopropoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3-Isopropoxypropylamine gave the title compound (5mg)

25 HPLC-MS (Conditions B) Retention time 2.37min MH<sup>+</sup> 549

**EXAMPLE 135**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-ethoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

30 3-Ethoxypropylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 535

**EXAMPLE 136**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-(3-indolyl)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

35

2-(3-indolyl)ethylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.15min MH<sup>+</sup> 592

**EXAMPLE 137**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclobutylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclobutylamine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.35min MH<sup>+</sup> 503

**EXAMPLE 138**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclopropylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclopropylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.26min MH<sup>+</sup> 489

**EXAMPLE 139**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-(1,2,3-thiadiazol-4-yl)benzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

4-(1,2,3-Thiadiazol-4-yl)benzylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.46 MH<sup>+</sup> 623

**EXAMPLE 140**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-nitrobenzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3-Nitrobenzylamine hydrochloride gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.46min MH<sup>+</sup> 584

**EXAMPLE 141**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-(methylsulfonyl)benzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

4-(Methylsulfonyl)benzylamine hydrochloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.31min MH<sup>+</sup> 617

**EXAMPLE 142**



(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-(benzylthio)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

2-(Benzylthio)ethylamine hydrochloride gave the title compound (7mg)

5 HPLC-MS (Conditions B) Retention time 2.56min MH<sup>+</sup> 599

EXAMPLE 143

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-(4-nitrophenyl)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

10

2-(4-Nitrophenyl)ethylamine hydrochloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.47min MH<sup>+</sup> 598

EXAMPLE 144

15 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-piperidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

Piperidine gave the title compound (5mg).

HPLC-MS (Conditions B) Retention time 2.36min MH<sup>+</sup> 517

20 EXAMPLE 145

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-morpholino-3,4-dioxocyclobut-1-enylamino]propanoic acid

Morpholine gave the title compound (7mg)

HPLC-MS (Conditions B) Retention time 2.24min MH<sup>+</sup> 519

25

EXAMPLE 146

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-thiomorpholino-3,4-dioxocyclobut-1-enylamino]propanoic acid

Thiomorpholine gave the title compound (1mg)

30 HPLC-MS (Conditions B) Retention time 2.36min MH<sup>+</sup> 535

EXAMPLE 147

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-diethylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid

35 Diethylamine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.34min MH<sup>+</sup> 505

**EXAMPLE 148**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

- 5 Pyrrolidine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.29min MH<sup>+</sup> 503

**EXAMPLE 149**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-ethyl-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

- 10 1-Ethylpiperazine gave the title compound (6mg)  
HPLC-MS (Conditions B) Retention time 1.96min MH<sup>+</sup> 546

**EXAMPLE 150**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-(hydroxypropyl)-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

- 15 1-Piperazinepropanol gave the title compound (6mg)  
HPLC-MS (Conditions B) Retention time 1.94min MH<sup>+</sup> 576  
20

**EXAMPLE 151**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((S)-3-dimethylamino-1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

- 25 (S)-3-(Dimethylamino)pyrrolidine gave the title compound (8mg)  
HPLC-MS (Conditions B) Retention time 1.94min MH<sup>+</sup> 546

**EXAMPLE 152**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((S)-2-(methoxymethyl)-1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid

- 30 (S)-2-(Methoxymethyl)pyrrolidine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.37min MH<sup>+</sup> 547

- 35 **EXAMPLE 153**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Piperazine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 1.93min MH<sup>+</sup> 518

5

**EXAMPLE 154**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((RS)-3-diethylamino-1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 3-(Diethylamino)pyrrolidine gave the title compound (6mg)

HPLC-MS (Conditions B) Retention time 1.98min MH<sup>+</sup> 574

**EXAMPLE 155**

15 **(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(4-(4-nitrophenyl)-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

1-(4-Nitrophenyl)piperazine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.54min MH<sup>+</sup> 639

20 **EXAMPLE 156**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-butylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Butylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.37min MH<sup>+</sup> 505

25

**EXAMPLE 157**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-pentylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Pentylamine gave the title compound (2mg)

30 HPLC-MS (Conditions B) Retention time 2.44min MH<sup>+</sup> 519

**EXAMPLE 158**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((RS)-1-methylpropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

35 1-Methylpropylamine gave the title compound (9mg)

HPLC-MS (Conditions B) Retention time 2.34min MH<sup>+</sup> 505

**EXAMPLE 159**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-isobutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 5 Isobutylamine gave the title compound (3mg)  
HPLC-MS (Conditions B) Retention time 2.35min MH<sup>+</sup> 505

**EXAMPLE 160**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-methyl-N-isopropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 10 Methylisopropylamine gave the title compound (4mg)  
HPLC-MS (Conditions B) Retention time 2.31min MH<sup>+</sup> 505

**EXAMPLE 161**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-ethyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 15 N-Ethylmethylamine gave the title compound (6mg)  
HPLC-MS (Conditions B) Retention time 2.26min MH<sup>+</sup> 491

**EXAMPLE 162**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-methyl-N-propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 20 N-Methylpropylamine gave the title compound (3mg)  
HPLC-MS (Conditions B) Retention time 2.32min MH<sup>+</sup> 505

**EXAMPLE 163**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclopropanemethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 25 Cyclopropanemethylamine gave the title compound (4mg)  
HPLC-MS (Conditions B) Retention time 2.32min MH<sup>+</sup> 503

**EXAMPLE 164**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(propynylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 35 2-Propynylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.26min MH<sup>+</sup> 487

**EXAMPLE 165**

5 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-isopentylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Isopentylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.44min MH<sup>+</sup> 519

**EXAMPLE 166**

10 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((RS)-2-methylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

2-Methylbutylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.42min MH<sup>+</sup> 519

15 **EXAMPLE 167**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((RS)-1,3-dimethylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

1,3-Dimethylbutylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.49min MH<sup>+</sup> 533

20

**EXAMPLE 168**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-methyl-N-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

N-Methylbutylamine gave the title compound (3mg)

25 HPLC-MS (Conditions B) Retention time 2.39min MH<sup>+</sup> 519

**EXAMPLE 169**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((RS)-1-methylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

30 1-Methylbutylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.41min MH<sup>+</sup> 519

**EXAMPLE 170**

35 (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-allylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Allylamine gave the title compound (3mg)



HPLC-MS (Conditions B) Retention time 2.27min MH<sup>+</sup> 489

**EXAMPLE 171**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(2-(methylthio)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

2-(Methylthio)ethylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.30min MH<sup>+</sup> 523

**EXAMPLE 172**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-carboxyethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

β-Alanine hydrochloride gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.19min MH<sup>+</sup> 521

**EXAMPLE 173**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((S)-1-carboxy-3-methylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

L-Leucine hydrochloride gave the title compound 0.5mg

HPLC-MS (Conditions B) Retention time 2.35min MH<sup>+</sup> 563

**EXAMPLE 174**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(carboxymethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

Glycine hydrochloride gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.19min MH<sup>+</sup> 507

**EXAMPLE 175**

(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((S)-1-carboxy-2-methylpropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

L-Valine hydrochloride gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.28min MH<sup>+</sup> 549

**EXAMPLE 176**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-((S)-1-carboxy-2-phenylethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

L-Phenylalanine gave the title compound (0.5mg)

5 HPLC-MS (Conditions B) Retention time 2.38min MH<sup>+</sup> 597

**EXAMPLE 177**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-ethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

10 Ethylamine hydrochloride gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.22min MH<sup>+</sup> 477

**EXAMPLE 178**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-methylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15 Methylamine hydrochloride gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.17 MH<sup>+</sup> 463

**EXAMPLE 179**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-dimethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20 Dimethylamine hydrochloride gave the title compound (6mg)

HPLC-MS (Conditions B) Retention time 2.20min MH<sup>+</sup> 477

**EXAMPLE 180**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-anilino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Derivatised resin (2), (320mg) in DMF (10ml), was treated with 4-anilino-3-ethoxy-3-cyclobutene-1,2-dione (400mg, 1.86mmol) for 12h at 70° then  
30 filtered and washed with DMF and DCM. The resin was treated with 60% trifluoroacetic acid in DCM (1.5ml) for 3h with agitation then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.46min MH<sup>+</sup> 525

35

**EXAMPLE 181**



**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-phenyl-3,4-dioxocyclobut-1-enylamino)propanoic acid**

By the same method as the compound of Example 180, 3-methoxy-4-phenyl-3-cyclobutene-1,2-dione was used to give the title compound (13mg).

HPLC-MS (Conditions B) Retention time 2.53min MH<sup>+</sup> 510

**EXAMPLE 182**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-methoxy-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Derivatised resin (3), (120mg) was treated with 60% trifluoroacetic acid in DCM (1.5ml) for 3h with agitation then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.26min MH<sup>+</sup> 465

**EXAMPLE 183**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-(1-decahydroquinolyl)-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Decahydroquinoline gave the title compound (1mg).

HPLC-MS (Conditions B) Retention time 2.53min MH<sup>+</sup> 571

**EXAMPLE 184**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-benzyl-N-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

N-Benzylbutylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.60min MH<sup>+</sup> 595

**EXAMPLE 185**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-(2-cyanoethyl)-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

N-Methyl-beta-alanine nitrile gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.22min MH<sup>+</sup> 516

**EXAMPLE 186**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-(2-(2-pyridyl)ethyl)-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

2-(2-Methylaminoethyl)pyridine gave the title compound (6mg)

5 HPLC-MS (Conditions B) Retention time 2.03min MH<sup>+</sup> 568

**EXAMPLE 187**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(1,2,3,6-tetrahydro-1-pyridyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 1,2,3,6-Tetrahydropyridine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.32min MH<sup>+</sup> 515

**EXAMPLE 188**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-methyl-N-(phenylethyl)amino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15 N-Methylphenylethylamine gave the title compound (6mg)

HPLC-MS (Conditions B) Retention time 2.45min MH<sup>+</sup> 567

**EXAMPLE 189**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N,N-dibutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

20 Dibutylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.58min MH<sup>+</sup> 561

25 **EXAMPLE 190**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3,3,3-trifluoropropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3,3,3-Trifluoropropylamine gave the title compound (7mg)

HPLC-MS (Conditions B) Retention time 2.35min MH<sup>+</sup> 545

30

**EXAMPLE 191**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-ethyl-N-(4-pyridylmethyl)amino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

35 4-(Ethylaminomethyl)pyridine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.01min MH<sup>+</sup> 568

**EXAMPLE 192**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(3-thiazolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 5 Thiazolidine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.29min MH<sup>+</sup> 521

**EXAMPLE 193**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-allyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 10 N-Methylallylamine gave the title compound (4mg)  
HPLC-MS (Conditions B) Retention time 2.29min MH<sup>+</sup> 503

**EXAMPLE 194**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-(N-benzyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 15 N-Benzylmethylamine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.42min MH<sup>+</sup> 553

**EXAMPLE 195**

**(S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-[2-N,N-iallylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

- 20 Diallylamine gave the title compound (5mg)  
HPLC-MS (Conditions B) Retention time 2.39min MH<sup>+</sup> 529.

**EXAMPLE 196**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-N,N-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 25 To the derivatised resin (8), (100mg) was added ethanol (1.0ml) and a 1M  
30 solution of diethylamine in DCM (0.7ml). The solution was agitated for 18h  
at RT then filtered and washed thoroughly with DCM. The resin was  
treated with 95% trifluoroacetic acid in DCM (2.0ml) for 3h with agitation  
and then filtered. The filtrate was evaporated *in vacuo* to give the crude  
product which was purified by preparative HPLC to afford the title  
35 compound (2mg).  
HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup> 459

The following compounds of Examples 197 to 237 were prepared in a similar manner to the compound of Example 196, each using the starting material shown. For examples where the amine was added as a salt, 1  
5 mol equivalent of DIPEA was also added.

**EXAMPLE 197**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-(3-methoxypropylamino)-3,4-dioxocyclobut-1-enylamino)propanoic acid**

10 3-Methoxypropylamine gave the title compound (4mg)  
HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup>475

**EXAMPLE 198**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(1-piperidiny)]-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15 Piperidine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 471

**EXAMPLE 199**

20 **(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(1-piperaziny)]-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Piperazine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 1.7min MH<sup>+</sup> 472

**EXAMPLE 200**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-pentylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

25 Pentylamine gave the title compound (3mg)  
HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 473

30

**EXAMPLE 201**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Propylamine gave the title compound (1mg)  
35 HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup> 445

**EXAMPLE 202**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-(1-decahydroquinolinyl)-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Decahydroquinoline gave the title compound (5mg)

5 HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 525

**EXAMPLE 203**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-{2-[N-ethyl-N-(4-pyridylmethyl)amino]-3,4-dioxocyclobut-1-enylamino}propanoic acid**

10 4-(Ethylaminomethyl)pyridine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 1.8min MH<sup>+</sup> 522

**EXAMPLE 204**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-tert-butylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 Tert-Butylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 459

**EXAMPLE 205**

20 **(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-cyclobutylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclobutylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 457

25 **EXAMPLE 206**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-thiomorpholino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Thiomorpholine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 489

30

**EXAMPLE 207**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-allylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Allylamine gave the title compound (0.3mg)

35 HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup> 443



**EXAMPLE 208**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(N-benzyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

N-Benzylmethylamine gave the title compound (5mg)

5 HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 507

**EXAMPLE 209**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-cyclohexylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

10 Cyclohexylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 485

**EXAMPLE 210**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-benzylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

15 Benzylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 493

**EXAMPLE 211**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-[3-(dimethylamino)propyl]amino-3,4-dioxocyclobut-1-enylamino)propanoic acid

20 3-(Dimethylamino)propylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 1.7min MH<sup>+</sup> 488

25 **EXAMPLE 212**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(2-pyridylmethyl)amino-3,4-dioxocyclobut-1-enylamino]propanoic acid

2-(Aminomethyl)pyridine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 1.9min MH<sup>+</sup> 494

30

**EXAMPLE 213**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(3-pyridylmethyl)amino-3,4-dioxocyclobut-1-enylamino]propanoic acid

3-(Aminomethyl)pyridine gave the title compound (1mg)

35 HPLC-MS (Conditions B) Retention time 1.8min MH<sup>+</sup> 494

**EXAMPLE 214**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(4-pyridylmethyl)amino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

4-(Aminomethyl)pyridine gave the title compound (5mg)

5 HPLC-MS (Conditions B) Retention time 1.8min MH<sup>+</sup> 494

**EXAMPLE 215**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(2-(benzylthio)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 2-(Benzylthio)ethylamine hydrochloride gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 553

**EXAMPLE 216**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-dimethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 Dimethylamine gave the title compound (24mg)

HPLC-MS (Conditions B) Retention time 1.9min MH<sup>+</sup> 431

**EXAMPLE 217**

20 **(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-morpholino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Morpholine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup> 473

25 **EXAMPLE 218**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(N-methyl-N-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

N-Methylbutylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 473

30

**EXAMPLE 219**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-[(RS)-2-methylbutylamino]-3,4-dioxocyclobut-1-enylamino]propanoic acid**

2-Methylbutylamine gave the title compound (4mg)

35 HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 473



**EXAMPLE 220**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-butylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Butylamine gave the title compound (4mg)

5 HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 459

**EXAMPLE 221**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-{2-[(RS)-1,3-dimethylbutylamino]-3,4-dioxocyclobut-1-enylamino}propanoic acid

10 1,3-Dimethylbutylamine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 487

**EXAMPLE 222**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(N-methyl-N-isopropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

15 Methylisopropylamine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 459

**EXAMPLE 223**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-{2-[(RS)-1-methylbutylamino]-3,4-dioxocyclobut-1-enylamino}propanoic acid

20 1-Methylbutylamine gave the title compound (6mg)

HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 473

**EXAMPLE 224**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-isobutylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Isobutylamine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 459

**EXAMPLE 225**

(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-(2-dipropylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Dipropylamine gave the title compound (4mg)

35 HPLC-MS (Conditions B) Retention time 2.2min MH<sup>+</sup> 487

**EXAMPLE 226**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-{2-[(RS)-2-methylpropylamino]-3,4-dioxocyclobut-1-enylamino}propanoic acid**

1-Methylpropylamine gave the title compound (4mg)

5 HPLC-MS (Conditions B) Retention time 2.1min MH<sup>+</sup> 459

**EXAMPLE 227**

**(S)-3-[4-(1-Isoquinolylamino)phenyl]-2-[2-(N-ethyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 N-Ethylmethylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.0min MH<sup>+</sup> 445

**EXAMPLE 228**

**(S)-3-[4-(2,3,4-Trimethoxybenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15

To the derivatised resin (5), (120mg) was added DCM (5ml), DIPEA (0.1ml, 0.6mmol) and 2,3,4-trimethoxybenzoyl chloride (138mg, 0.6mmol). The solution was agitated for 12h at RT then filtered and washed thoroughly with DCM. The resin was treated with 60% trifluoroacetic acid in DCM (1.5ml) for 3h with agitation and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (0.5mg).

20

HPLC-MS (Conditions B) Retention time 2.34min MH<sup>+</sup> 512

25 The following compounds of Examples 229 to 241 were prepared in a similar manner to the compound of Example 228, each using the starting material shown.

**EXAMPLE 229**

**(S)-3-[4-(2,4-Dimethoxybenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

30

2,4-Dimethoxybenzoylchloride gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.41min MH<sup>+</sup> 482

35 **EXAMPLE 230**

**(S)-3-[4-(4-Bromobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

4-Bromobenzoylchloride gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.49min MH<sup>+</sup> 500

5

**EXAMPLE 231**

**(S)-3-[4-(2-Thienylcarbonylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Thiophene-2-carbonylchloride gave the title compound (0.5mg)

10 HPLC-MS (Conditions B) Retention time 2.31min MH<sup>+</sup> 428

**EXAMPLE 232**

**(S)-3-[4-(trans-Cinnamoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 trans-Cinnamoylchloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.44min MH<sup>+</sup> 448

**EXAMPLE 233**

**(S)-3-[4-(Phenylacetylaminophenyl)-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20 Phenacetylchloride gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.34min MH<sup>+</sup> 436

**EXAMPLE 234**

25 **(S)-3-[4-(2,6-Dichlorobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

2,6-Dichlorobenzoylchloride gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.39min MH<sup>+</sup> 490

30 **EXAMPLE 235**

**(S)-3-[4-(2,6-Dimethylbenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

2,6-Dimethylbenzoylchloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.38min MH<sup>+</sup> 450

35

**EXAMPLE 236**

**(S)-3-[4-(Benzyloxyacetyl amino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Benzyloxyacetylchloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.41min MH<sup>+</sup> 466

5

**EXAMPLE 237**

**(S)-3-[4-(4-Cyanobenzoyl amino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

4-Cyanobenzoylchloride gave the title compound (1mg)

10 HPLC-MS (Conditions B) Retention time 2.33min MH<sup>+</sup> 447

**EXAMPLE 238**

**(S)-3-[4-(6-Chloro-3-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 6-Chloronicotinyllchloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 457

**EXAMPLE 239**

**(S)-3-[4-(2-Chloro-3-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

20

2-Chloronicotinyllchloride gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.18min MH<sup>+</sup> 457

**EXAMPLE 240**

**(S)-3-[4-(2-Fluorobenzoyl amino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

25

2-Fluorobenzoylchloride gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.33min MH<sup>+</sup> 440

**EXAMPLE 241**

**(S)-3-[4-(3,4-Dimethoxybenzoyl amino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

30

3,4-Dimethoxybenzoylchloride gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.28min MH<sup>+</sup> 482

35

**EXAMPLE 242**

**(S)-3-[4-(4-Methoxyphenoxy)carbonylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- To the derivatised resin (5), (120mg) was added 1,4-dioxan (4.5ml), DIPEA (0.2ml, 1.2mmol), water (0.5ml) and 4-methoxyphenylchloroformate (0.2ml, 0.6mmol). The solution was agitated for 12h at RT then filtered and washed thoroughly with DCM. The resin was treated with 60% trifluoroacetic acid in DCM (1.5ml) for 3h with agitation and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (2mg).
- 10 HPLC-MS (Conditions B) Retention time 2.42min MH<sup>+</sup> 468

The following compounds of Examples 243 to 246 were prepared in a similar manner to the compound of Example 242, each using the starting material shown.

15

**EXAMPLE 243**

**(S)-3-[4-(4-Methylphenoxy)carbonylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- p-Tolylchloroformate gave the title compound (0.5mg)
- 20 HPLC-MS (Conditions B) Retention time 2.50min MH<sup>+</sup> 452

**EXAMPLE 244**

**(S)-3-[4-(4-Fluorophenoxy)carbonylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 25 4-Fluorophenylchloroformate gave the title compound (2mg)
- HPLC-MS (Conditions B) Retention time 2.45min MH<sup>+</sup> 456

**EXAMPLE 245**

**(S)-3-[4-(Phenoxy)carbonylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 30 Phenylchloroformate gave the title compound (2mg)
- HPLC-MS (Conditions B) Retention time 2.42min MH<sup>+</sup> 438

**EXAMPLE 246**

- 35 **(S)-3-[4-(4-Nitrobenzyloxy)carbonylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

4-Nitrobenzylchloroformate gave the title compound (1mg)  
HPLC-MS (Conditions B) Retention time 2.47min MH<sup>+</sup> 497

#### **EXAMPLE 247**

5 **(S)-3-(4-Benzoylphenyl)-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

To the derivatised resin (9), (200mg) was added ethanol (1.6ml), DCM (0.4ml) and propylamine (0.08ml, 1mmol). The solution was agitated for 12h at RT then filtered and washed thoroughly with DCM. The resin was  
10 treated with 95% trifluoroacetic acid in DCM (2.0ml) for 3h with agitation and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (4mg).

HPLC-MS (Conditions B) Retention time 2.4min MH<sup>+</sup> 407.

15

The following compound of Example 248 was prepared in a similar manner to the compound of Example 247 using the starting material shown.

#### **EXAMPLE 248**

20 **(S)-3-(4-Benzoylphenyl)-2-(2-morpholino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Morpholine gave the title compound (5mg)

HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 435

25 **EXAMPLE 249**

**(S)-3-[4-(1-Isoquinolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

A slurry of derivatised resin (5) (prepared from Wang resin (0.7mmol/g), 100mg) in DCM (5ml) was treated with 1-isoquinoline carboxylic acid (56mg, 0.30mmol), DIEA (45μl, 0.25mmol) and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-Tetramethyluronium-hexafluorophosphate] (HATU) (95mg, 0.25mmol). The mixture was agitated for 16h at RT then filtered and washed thoroughly with DCM, DMF, MeOH, DMF then DCM. The resin  
30 was treated with 50% trifluoroacetic acid in DCM (5ml) for 3h with agitation and then filtered. The resin was washed with a further portion of DCM (5ml). The combined filtrate was evaporated *in vacuo* to give the crude  
35



product which was purified by preparative HPLC to afford the title compound (7.3mg).

HPLC-MS (Conditions B). Retention time 2.47min,  $MH^+$  473

- 5 The following compounds of Examples 250 to 281 were prepared in a similar manner to the compound of Example 249, each using the starting material shown.

**EXAMPLE 250**

- 10 **(S)-3-[4-[2-Benzo(b)furan]carboxamido]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

2-Benzo(b)furan carboxylic acid gave the title compound (4.0mg)

HPLC-MS (Conditions B). Retention time 2.45min,  $MH^+$  462

- 15 **EXAMPLE 251**

**(S)-3-[4-(4-Methoxy-2-quinolyl)carboxamido]phenyl]-2-(2-propylamino-3,4-dioxo cyclobut-1-enylamino)propanoic acid**

4-Methoxy-2-quinoline carboxylic acid gave the title compound (5.3mg)

HPLC-MS (Conditions B). Retention time 2.59min,  $MH^+$  503

20

**EXAMPLE 252**

**(S)-3-[4-[4-Oxo-4, 5, 6, 7-tetrahydrobenzo(b)furan-3-yl]carboxamido]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 25 4-Oxo-4, 5, 6, 7-tetrahydrobenzo(b)furan-3-carboxylic acid gave the title compound (8.2mg)

HPLC-MS (Conditions B). Retention time 2.37min,  $MH^+$  480

**EXAMPLE 253**

- 30 **(S)-3-[4-(2-(1-Pyrrolyl)-5-pyridyl)carboxamido]phenyl]-2-(2-propylamino-3,4-dioxocyclo but-1-enylamino)propanoic acid**

2-(1-Pyrrolyl)-5-pyridine carboxylic acid gave the title compound (1.7mg)

HPLC-MS (Conditions B). Retention time 2.45min,  $MH^+$  488

- 35 **EXAMPLE 254**



**(S)-3-[4-(3-Indazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

3-Indazolecarboxylic acid gave the title compound (5.0mg)

HPLC-MS (Conditions B). Retention time 2.34min, MH<sup>+</sup> 462

5

**EXAMPLE 255**

**(S)-3-[4-(4-Fluorobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

4-Fluorobenzoic acid gave the title compound (3.7mg)

10 HPLC-MS (Conditions B). Retention time 2.37min, MH<sup>+</sup> 440

**EXAMPLE 256**

**(S)-3-[4-(4-Methoxybenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

15 4-Methoxybenzoic acid gave the title compound (0.3mg)

HPLC-MS (Conditions B). Retention time 2.34min, MH<sup>+</sup> 452

**EXAMPLE 257**

**(S)-3-[4-(4-Acetamidobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

20 4-Acetamidobenzoic acid gave the title compound (3.7mg)

HPLC-MS (Conditions B). Retention time 2.16min, MH<sup>+</sup> 479

**EXAMPLE 258**

25 **(S)-3-[4-(4-Acetylbenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

4-Acetylbenzoic acid gave the title compound (2.0mg)

HPLC-MS (Conditions B). Retention time 2.28min, MH<sup>+</sup> 461

30 **EXAMPLE 259**

**(S)-3-[4-(4-Nitrobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

4-Nitrobenzoic acid gave the title compound (4.3mg)

HPLC-MS (Conditions B). Retention time 2.39min, MH<sup>+</sup> 467

35

**EXAMPLE 260**

**(S)-3-[4-[4-(4-Hydroxyphenyl)benzoylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

4-Hydroxybiphenyl carboxylic acid gave the title compound (0.8mg)  
HPLC-MS (Conditions B). Retention time 2.36min, MH<sup>+</sup> 514

5

**EXAMPLE 261**

**(S)-3-[4-(4-Cyanobenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

4-Cyanobenzoic acid gave the title compound (6.5mg)

10 HPLC-MS (Conditions B). Retention time 2.32min, MH<sup>+</sup> 447

**EXAMPLE 262**

**(S)-3-[4-(4-Trifluoromethylbenzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 4-Trifluoromethylbenzoic acid gave the title compound (5.4mg)

HPLC-MS (Conditions B). Retention time 2.55min, MH<sup>+</sup> 560

**EXAMPLE 263**

**(S)-3-[4-(N-Oxo-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

20 4-Pyridyl-N-oxide carboxylic acid gave the title compound (4.7mg)

HPLC-MS (Conditions B). Retention time 1.97min, MH<sup>+</sup> 439

**EXAMPLE 264**

25 **(S)-3-[4-(2, 6-Dichloro-3-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

2, 6, Dichloronicotinic acid gave the title compound (4.7mg)

HPLC-MS (Conditions B). Retention time 2.31min, MH<sup>+</sup> 493

30 **EXAMPLE 265**

**(S)-3-[4-(2-(Methoxycarbonyl)benzoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

2-Methoxycarbonylbenzoic acid gave the title compound (3.4mg)

HPLC-MS (Conditions B). Retention time 2.28min, MH<sup>+</sup> 480

35

**EXAMPLE 266**

**(S)-3-[4-[5-Methyl-2-(trifluoromethyl)-3-furanylcarboxamido]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

5-Methyl-2-(trifluoromethyl)-3-furancarboxylic acid gave the title compound (5.6mg)

5 HPLC-MS (Conditions B). Retention time 2.48min, MH<sup>+</sup> 494

**EXAMPLE 267**

**(S)-3-[4-(2-Acetyl-3-thienylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

10 2-Acetyl-3-thiophenecarboxylic acid gave the title compound (5.2mg)

HPLC-MS (Conditions B). Retention time 2.28min, MH<sup>+</sup> 470

**EXAMPLE 268**

**(S)-3-[4-[(R)-2-Oxothiazolidin-4-ylcarboxamido]phenyl]-2-(2-propylamino-3,4-dioxo cyclobut-1-enylamino)propanoic acid**

15 (R)-2-Oxothiazolidine-4-carboxylic acid gave the title compound (5.4mg)

HPLC-MS (Conditions B). Retention time 2.07min, MH<sup>+</sup> 447

**EXAMPLE 269**

20 **(S)-3-[4-(4-Nitro-3-pyrazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

4-Nitro-3-pyrazolecarboxylic acid gave the title compound (3.0mg)

HPLC-MS (Conditions B). Retention time 2.14min, MH<sup>+</sup> 457

25 **EXAMPLE 270**

**(S)-3-[4-(5-Chloro-2-thienylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

5-Chloro-2-thiophenecarboxylic acid gave the title compound (5.3mg)

HPLC-MS (Conditions B). Retention time 2.48min, MH<sup>+</sup> 462

30

**EXAMPLE 271**

**(S)-3-[4-(1-Methyl-5-nitro-4-pyrazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

1-Methyl-5-nitro-4-pyrazolecarboxylic acid gave the title compound (6.1mg)

35

HPLC-MS (Conditions B). Retention time 2.23min, MH<sup>+</sup> 471

**EXAMPLE 272**

**(S)-3-[4-(2-Furoylamino)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino) propanoic acid**

- 5 2-Furoic acid gave the title compound (3.7mg)  
HPLC-MS (Conditions B). Retention time 2.23min, MH<sup>+</sup> 412

**EXAMPLE 273**

**(S)-3-[4-(2, 4-Dimethyl-5-thiazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxo cyclobut-1-enylamino)propanoic acid**

- 10 2, 4-Dimethyl-5-thiazolecarboxylic acid gave the title compound (4.2mg)  
HPLC-MS (Conditions B). Retention time 2.18min, MH<sup>+</sup> 457

**EXAMPLE 274**

**(S)-3-[4-(1, 2, 3-thiadiazol-4-ylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxo cyclobut-1-enylamino)propanoic acid**

- 15 1, 2, 3, Thiadiazole-5-carboxylic acid gave the title compound (4.9mg)  
HPLC-MS (Conditions B). Retention time 2.20min, MH<sup>+</sup> 430

**EXAMPLE 275**

**(S)-3-[4-(2-Thienylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 20 2-Thiophenecarboxylic acid gave the title compound (5.0mg)  
HPLC-MS (Conditions B). Retention time 2.31min, MH<sup>+</sup> 428

**EXAMPLE 276**

**(S)-3-[4-(2-Pyrazinylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl amino)propanoic acid**

- 25 2-Pyrazinecarboxylic acid gave the title compound (4.2mg)  
30 HPLC-MS (Conditions B). Retention time 2.16min, MH<sup>+</sup> 424

**EXAMPLE 277**

**(S)-3-[4-[(2-Furyl)oxalylamino]phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

- 35  $\alpha$ -Oxo-2-furanacetic acid gave the title compound (4.8mg)  
HPLC-MS (Conditions B). Retention time 2.3min, MH<sup>+</sup> 440.

**EXAMPLE 278**

**(S)-3-[4-(3-Methyl-2-thienylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-en-1-ylamino)propanoic acid**

- 5 3-Methyl-2-thiophenecarboxylic acid gave the title compound (2.0mg)  
HPLC-MS (Conditions B). Retention time 2.37min, MH<sup>+</sup> 442

**EXAMPLE 279**

**(S)-3-[4-(4-Methyl-1,2,3-thiadiazol-5-ylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-en-1-ylamino)propanoic acid**

- 10 4-Methyl-1,2,3-thiazole-5-carboxylic acid gave the title compound (4.0mg)  
HPLC-MS (Conditions B). Retention time 2.24min, MH<sup>+</sup> 444

**EXAMPLE 280**

**(S)-3-[4-(5-Phenyl-4-oxazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-en-1-ylamino)propanoic acid**

- 15 5-Phenyl-4-oxazolecarboxylic acid gave the title compound (5.9mg)  
HPLC-MS (Conditions B). Retention time 2.51min, MH<sup>+</sup> 489

**EXAMPLE 281**

**(S)-3-[4-(3-Methyl-5-trifluoromethyl-4-isoxazolylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-en-1-ylamino)propanoic acid**

- 20 3-Methyl-5-trifluoromethyl-4-isoxazolecarboxylic acid gave the title compound (5.8mg)  
25 HPLC-MS (Conditions B). Retention time 2.43min, MH<sup>+</sup> 495.

The following compounds of Examples 282 to 323 were prepared in a similar manner to the compound of Example 105, using derivatised resin (4) and the starting material shown. For examples where the amine was  
30 added as a salt 1 mol equivalent of DIPEA was also added.

**EXAMPLE 282**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-morpholinoethylamino)-3,4-dioxocyclobut-1-en-1-ylamino]propanoic acid**

- 35 acid  
N-(2-Aminoethyl)morpholine gave the title compound (2mg)



HPLC-MS (Conditions B) Retention time 1.98min MH<sup>+</sup> 562

**EXAMPLE 283**

5 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-piperidinoethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
1-(2-Aminoethyl)piperidine gave the title compound (2mg)  
HPLC-MS (Conditions B) Retention time 2.02min MH<sup>+</sup> 560

**EXAMPLE 284**

10 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-(2-oxopyrrolidin-1-yl)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
1-(3-Aminopropyl)-2-pyrrolidinone gave the title compound (1mg)  
HPLC-MS (Conditions B) Retention time 2.14min MH<sup>+</sup> 574

15 **EXAMPLE 285**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-(1-imidazolyl)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
20 N-(3-Aminopropyl)imidazole gave the title compound (3mg)  
HPLC-MS (Conditions B) Retention time 1.98min MH<sup>+</sup> 557

**EXAMPLE 286**

25 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(1-benzyl-4-piperidinylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
4-Amino-1-benzylpiperidine gave the title compound (6mg)  
HPLC-MS (Conditions B) Retention time 2.13min MH<sup>+</sup> 622

**EXAMPLE 287**

30 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-pyridylmethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid  
2-(Aminomethyl)pyridine gave the title compound (6mg)  
HPLC-MS (Conditions B) Retention time 2.17min MH<sup>+</sup> 540

35 **EXAMPLE 288**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-pyridylmethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3-(Aminomethyl)pyridine gave the title compound (3mg)

HPLC-MS (Conditions B) Retention time 2.07min MH<sup>+</sup> 540

5

**EXAMPLE 289**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3,3-dimethylbutylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3,3-Dimethylbutylamine gave the title compound (3mg)

10 HPLC-MS (Conditions B) Retention time 2.45min MH<sup>+</sup> 533

**EXAMPLE 290**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3,4-dichlorobenzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15 3,4-Dichlorobenzylamine gave the title compound (4mg)

HPLC-MS (Conditions B) Retention time 2.51min MH<sup>+</sup> 607

**EXAMPLE 291**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-(1-piperazinyl)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

20

N-(2-Aminoethyl)piperazine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 1.97min MH<sup>+</sup> 561

25 **EXAMPLE 292**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-isopropylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Isopropylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.25min MH<sup>+</sup> 491

30

**EXAMPLE 293**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-propylamino-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Propylamine gave the title compound (2mg)

35 HPLC-MS (Conditions B) Retention time 2.25min MH<sup>+</sup> 491



**EXAMPLE 294**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-tert-butylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Tert-Butylamine gave the title compound (0.5mg)

5 HPLC-MS (Conditions B) Retention time 2.33min MH<sup>+</sup> 505

**EXAMPLE 295**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-benzylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

10 Benzylamine gave the title compound (1mg)

HPLC-MS (Conditions B) Retention time 2.37min MH<sup>+</sup> 539

**EXAMPLE 296**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-(dimethylamino)propylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

15

3-(Dimethylamino)propylamine gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 1.89min MH<sup>+</sup> 534

20 **EXAMPLE 297**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-isopropoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

3-Isopropoxypropylamine gave the title compound (1mg)

25 HPLC-MS (Conditions B) Retention time 2.3min MH<sup>+</sup> 549

**EXAMPLE 298**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-ethoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

30 3-Ethoxypropylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.23min MH<sup>+</sup> 535

**EXAMPLE 299**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-methoxyethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

35

2-Methoxyethylamine gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.16min MH<sup>+</sup> 507

**EXAMPLE 300**

5 **(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(3-methoxypropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

3-Methoxypropylamine gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.18min MH<sup>+</sup> 521

**EXAMPLE 301**

10 **(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-cyclobutylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclobutylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.28min MH<sup>+</sup> 503

15 **EXAMPLE 302**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-cyclopropylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclopropylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.19min MH<sup>+</sup> 489

20

**EXAMPLE 303**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(2-(benzylthio)ethylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

25 2-(Benzylthio)ethylamine hydrochloride gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.46min MH<sup>+</sup> 599

**EXAMPLE 304**

30 **(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(4-(1,2,3-thiadiazol-4-yl)benzylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

4-(1,2,3-Thiadiazol-4-yl)benzylamine gave the title compound (2mg)

HPLC-MS (Conditions B) Retention time 2.38min MH<sup>+</sup> 623

35 **EXAMPLE 305**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-cyclohexylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Cyclohexylamine gave the title compound (0.5mg)

HPLC-MS (Conditions B) Retention time 2.39min MH<sup>+</sup> 531

5

**EXAMPLE 306**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-piperidiny-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Piperidine gave the title compound (2mg)

10 HPLC-MS (Conditions A) Retention time 2.32min MH<sup>+</sup> 517

**EXAMPLE 307**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-thiomorpholino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

15 Thiomorpholine gave the title compound (1mg)

HPLC-MS (Conditions A) Retention time 2.32min MH<sup>+</sup> 535

**EXAMPLE 308**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(4-methyl-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

20 1-Methylpiperazine gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 1.93min MH<sup>+</sup> 532

**EXAMPLE 309**

25 **(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-diethylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

Diethylamine gave the title compound (2mg)

HPLC-MS (Conditions A) Retention time 2.29min MH<sup>+</sup> 505

30 **EXAMPLE 310**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

Pyrrolidine gave the title compound (1mg)

HPLC-MS (Conditions A) Retention time 2.24min MH<sup>+</sup> 503

35

**EXAMPLE 311**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(4-ethyl-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

1-Ethylpiperazine gave the title compound (1mg)

HPLC-MS (Conditions A) Retention time 1.94min MH<sup>+</sup> 546

5

**EXAMPLE 312**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(4-(hydroxypropyl)-1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

10 1-Piperazinepropanol gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 1.93min MH<sup>+</sup> 576

**EXAMPLE 313**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(1-piperazinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

15

Piperazine gave the title compound (4mg)

HPLC-MS (Conditions A) Retention time 1.92min MH<sup>+</sup> 518

**EXAMPLE 314**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-((S)-3-dimethylamino-1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

20

(S)-3-(Dimethylamino)pyrrolidine gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 1.92min MH<sup>+</sup> 546

25

**EXAMPLE 315**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-((RS)-3-diethylamino-1-pyrrolidinyl)-3,4-dioxocyclobut-1-enylamino]propanoic acid**

30 3-(Diethylamino)pyrrolidine gave the title compound (3mg)

HPLC-MS (Conditions A) Retention time 1.95min MH<sup>+</sup> 574

**EXAMPLE 316**

**(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-butylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid**

35

Butylamine gave the title compound (0.1mg)

HPLC-MS (Conditions A) Retention time 2.33min MH<sup>+</sup> 505

**EXAMPLE 317**

5 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-pentylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Pentylamine gave the title compound (1mg)

HPLC-MS (Conditions A) Retention time 2.40min MH<sup>+</sup> 519

10 EXAMPLE 3198(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-((RS)-2-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

1-Methylpropylamine gave the title compound (2mg)

HPLC-MS (Conditions A) Retention time 2.31min MH<sup>+</sup> 505

15 **EXAMPLE 319**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-(2-isobutylamino-3,4-dioxocyclobut-1-enylamino)propanoic acid

Isobutylamine gave the title compound (2mg)

HPLC-MS (Conditions A) Retention time 2.31min MH<sup>+</sup> 505

20

**EXAMPLE 320**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(N-methyl-N-isopropylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

Methylisopropylamine gave the title compound (2mg)

25 HPLC-MS (Conditions A) Retention time 2.3min MH<sup>+</sup> 505

**EXAMPLE 321**

(RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(N-ethyl-N-methylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

30 N-Ethylmethylamine gave the title compound (0.2mg)

HPLC-MS (Conditions A) Retention time 2.24min MH<sup>+</sup> 491

**EXAMPLE 322**

35 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(N-methyl-N-butylamino)-3,4-dioxocyclobut-1-enylamino]propanoic acid

N-Methylbutylamine gave the title compound (0.3mg)

HPLC-MS (Conditions A) Retention time 2.38min MH<sup>+</sup> 519

**EXAMPLE 323**

5 (RS)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[2-(N-ethyl-N-(pyridylmethyl)amino]-3,4-dioxocyclobut-1-enylamino]propanoic acid  
4-(Ethylaminomethyl)pyridine gave the title compound (1mg)  
HPLC-MS (Conditions A) Retention time 2.01min MH<sup>+</sup> 568

**EXAMPLE 324**

10 3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-isopropylamino-3,4-dioxocyclobut-1-enylamino)prop-2-enoic acid

Derivatised resin 6 (1.0g) was treated with the Intermediate 44 (0.4g, 3.0mmol) and a catalytic amount of dirhodiumtetraacetate in toluene (10ml) at 120° for 2.5h. The resin was then filtered and washed with DMF  
15 and DCM to give resin bound  $\alpha$ -(2-methoxy-3,4-dioxocyclo-but-1-enylamino)diethylphosphonoacetate. This resin was then treated with 4-(3,5-dichloro-4-pyridylcarboxamido)benzaldehyde (0.53g, 1.8mmol) and diazabicycloundec-7-ene (DBU) (0.1g, 1.2mmol) in DCM (5.0ml). The mixture was agitated at ambient temperature for 72h then filtered and the  
20 resin washed thoroughly with DCM. A 90mg portion of this resin was treated with 2-propylamine (0.045mL, 0.6mmol), in DCM (0.2mL) and MeOH (0.8mL). The mixture was agitated at ambient temperature for 16h then filtered and washed thoroughly with DCM, MeOH, DMF, MeOH and DCM. The resin was treated with 50% trifluoroacetic acid in DCM (2ml) for  
25 3h with agitation and then filtered. The resin was washed with a further portion of DCM (2ml) and the combined filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (0.9mg).

30 HPLC-MS (Conditions B). Retention time 2.29min, MH<sup>+</sup> 489

The following compound of Example 325 was prepared in an identical manner to the compound of Example 324, using the starting material shown.

35

**EXAMPLE 325**



**3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-cyclobutylamino-3,4-dioxocyclobut-1-enylamino)prop-2-enoic acid**

Cyclobutylamine gave the title compound (0.4mg)  
HPLC-MS (Conditions B). Retention time 2.33min, MH<sup>+</sup> 501.

5

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC<sub>50</sub> value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

**$\alpha_4\beta_1$  Integrin-dependent Jurkat cell adhesion to VCAM-Ig**

96 well NUNC plates were coated with F(ab)<sub>2</sub> fragment goat anti-human IgG Fc $\gamma$ -specific antibody [Jackson Immuno Research 109-006-098: 100  $\mu$ l at 2  $\mu$ g/ml in 0.1M NaHCO<sub>3</sub>, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at RT on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at RT on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200  $\mu$ l containing 2.5 x 10<sup>5</sup> Jurkat cells in the presence or absence of titrated test compounds.

25

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 $\mu$ l MeOH for 10 minutes followed by another wash. 100 $\mu$ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at RT and the plates washed (3x) in PBS. 100 $\mu$ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

**$\alpha_4\beta_7$  Integrin-dependent JY cell adhesion to MAdCAM-Ig**

This assay was performed in the same manner as the  $\alpha_4\beta_1$  assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the  $\beta$ -lympho blastoid cell-line JY was used in place of Jurkat cells.

35



The IC<sub>50</sub> value for each test compound was determined as described in the  $\alpha_4\beta_1$  integrin assay.

**$\alpha_5\beta_1$  Integrin-dependent K562 cell adhesion to fibronectin**

- 5 96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 $\mu$ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 $\mu$ l PBS/1% BSA at RT on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total  
10 volume of 200 $\mu$ l containing 2.5x 10<sup>5</sup> K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the  $\alpha_4\beta_1$  assay above.

15  **$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic**

- 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10<sup>5</sup> freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 $\mu$ l in the  
20 presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at RT. The plates were washed in medium and 100 $\mu$ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were  
25 then left on a rocker at RT for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H<sub>2</sub>O<sub>2</sub> (Sigma) and 50 $\mu$ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

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**$\alpha_{IIb}/\beta_3$ -dependent human platelet aggregation**

- Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood  
35 anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10<sup>8</sup>/ml in autologous plasma. Cuvettes

contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl<sub>2</sub>.H<sub>2</sub>O 0.427; CaCl<sub>2</sub> 0.2; KCl 0.2; D-glucose 1.0; NaHCO<sub>3</sub> 1.0; NaHPO<sub>4</sub>.2H<sub>2</sub>O 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

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In the above assays the preferred compounds of the invention in which R<sup>1</sup> is an α<sub>4</sub> integrin binding group, such as the compounds of the Examples generally have IC<sub>50</sub> values in the α<sub>4</sub>β<sub>1</sub> and α<sub>4</sub>β<sub>7</sub> assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC<sub>50</sub> values of 50μM and above thus demonstrating the potency and selectivity of their action against α<sub>4</sub> integrins.

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The following assays may be used to determine the ability of compounds according to the invention to inhibit α<sub>v</sub>β<sub>3</sub> and α<sub>v</sub>β<sub>5</sub> function.

15

#### α<sub>v</sub>β<sub>3</sub> -Dependent Direct Binding Assay

96 Well NUNC immunoplates were coated overnight with a non-blocking anti-β<sub>3</sub> monoclonal antibody at 2 μg/ml in Dulbecco's phosphate buffered saline (PBS) and subsequently blocked with 5% 9<sup>w</sup>/<sub>v</sub>)BSA in PBS (Sigma, fraction V) for 60 min. at RT. After washing in Tris-buffered saline (TBS: 20mM Tris/150 mM NaCl, pH 7.5), plates then received 100μl of a lysate prepared from JY cells and were incubated for 3h at RT. The lysate was made by lysing JY B-lymphoblastoid cells at 5 x 10<sup>7</sup> cells were ml in TBS containing 1 mM MnCl<sub>2</sub>, 1% (v/v) BSA/0.1% (v/v) Tween 20 and were incubated for a further 2 hours at RT. Inhibitors were titrated into the fibronectin prior to addition to plates. After washing, streptavidin-peroxidase (Amersham) at 1:500 in TBS/1% (w/v) BSA/0.1% (v/v) Tween 20 was added and plates incubated for 1h at RT. Finally 100μl TMB substrate was added and Absorbance (630nm) measured after 10-15 minutes. IC<sub>50</sub> values for inhibition of adhesion were calculated on the Activity Base curve fitting programme.

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25

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#### α<sub>v</sub>β<sub>3</sub> -Dependent Cell Adhesion Assay

This was a modification of a published method [Stupack *et al.*, Exp. Cell. Res. 203, 443-448 (1992)] and employed the JY cell line. These cells are maintained in RPMI 1640 + 10% FCS + 2mM L-glutamine and, when used

35

for assay, were washed in assay medium (RPMI 1640 + 10% FCS),  
suspended at  $4 \times 10^6$ /ml in the same medium and pretreated with a  
blocking monoclonal antibody to CD18 (6.5E, F(ab')<sub>2</sub> fragment) for 10 min  
at RT. 96 Well NUNC immunoplates were coated with 100 $\mu$ l 2.5 $\mu$ g/ $\mu$ l  
5 human vitronectin in PBS per well for 2h at 37°C; they were then washed  
2x in PBS and blocked with 1% (w/v) BSA in PBS for 60min at RT and  
washed 2x more in PBS.  $2 \times 10^5$  JY per well were added to wells  
containing compounds serially titrated across the plate and, finally,  
phorbol-12-myristate-13-acetate at 10ng/ml was added in a final volume of  
10 200 $\mu$ l. After incubation at 37°C for 30min, non-adherent cells were  
removed by washing 3 x in assay medium, adherent cells were fixed in  
MeOH and stained with 0.25% (w/v) Rose Bengal in PBS for 5 min,  
unbound dye was removed by 3 further washes in PBS and cell-bound dye  
was released with 1:1 PBS:ethanol. Absorbance at 570nm was then  
15 measured. IC<sub>50</sub> values for inhibition of adhesion were calculated as  
described above for the direct binding assay.

#### $\alpha_v\beta_5$ -Dependent Cell Adhesion Assay

This assay was based on a published method [Koivunen *et al*, J. Bio.  
20 Chem. 268, 20205-20210 (1993)] and employed the human colon  
adenocarcinoma cell line HT-29. HT-29 Cells were routinely maintained in  
DMEM + 10% FCS + 2mM L-glutamine and were removed from flasks  
using trypsin/EDTA, washed 2x in assay medium and suspended at  $4 \times$   
 $10^6$ /ml in the same medium. The cells were allowed to 'rest' for 15 min. at  
25 RT before being added ( $2 \times 10^5$ /well) to wells containing compounds  
serially titrated across the plate in a final volume of 200 $\mu$ l. The 96 well  
NUNC immunoplates had been coated with human vitronectin as  
described above for the  $\alpha_v\beta_3$  assay. After incubation at 37°C for 60min,  
adhesion was assessed as described above for the  $\alpha_v\beta_3$  assay.

30

In the above assays the preferred compounds of the invention generally  
have IC<sub>50</sub> values of 1 $\mu$ M and below.

The advantageous clearance properties of compounds according to the  
35 invention may be demonstrated as follows:

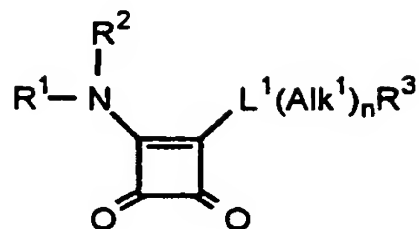
- Hepatic clearance, whether metabolic or biliary, can make a substantial contribution to the total plasma clearance of a drug. The total plasma clearance is a principal parameter of the pharmacokinetic properties of a medicine. It has a direct impact on the dose required to achieve effective plasma concentrations and has a major impact on the elimination half-life and therefore the dose-interval. Furthermore, high hepatic clearance is an indicator of high first-pass hepatic clearance after oral administration and therefore low oral bioavailability.
- 5
- 10 Many peptidic and non-peptidic carboxylic acids of therapeutic interest are subject to high hepatic clearance from plasma. Except for drugs which function in the liver, hepatic uptake from blood or plasma is undesirable because it leads to high hepatic clearance if the compound is excreted in bile or metabolised, or if the substance is not cleared from the liver, it may
- 15 accumulate in the liver and interfere with the normal function of the liver.

- The total plasma clearance of a compound according to the invention can be determined as follows:
- a small dose of the compound in solution is injected into a vein of a test
- 20 animal. Blood samples are withdrawn from a blood vessel of the animal at several times after the injection, and the concentration of compound in the bleed or plasma is measured using a suitable assay. The area under the curve (AUC<sub>iv</sub>) is calculated by non-compartmental methods (for example, the trapezium method) or by pharmacokinetic modelling. The total plasma
- 25 clearance (CL<sub>p</sub>) is calculated by dividing the *intravenous* dose(D<sub>iv</sub>) by the AUC<sub>iv</sub> for the blood plasma concentration - time course of a drug administered by the *intravenous* route:  $CL_p = D_{iv} \div AUC_{iv}$

- When tested in this manner, compounds according to the invention are not
- 30 rapidly or extensively extracted by the liver and have low total plasma clearance where low is defined as less than 10 ml/min/kg in the laboratory rat (Sprague Dawley CD). This compares favourably with functionally equivalent integrin binding compounds in which the squaric acid framework of compounds of formula (1) is not present.

**CLAIMS**

1. A compound of formula (1):



(1)

wherein

R<sup>1</sup> is an integrin binding group;

R<sup>2</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl group;

L<sup>1</sup> is a covalent bond or a linker atom or group;

n is zero or the integer 1;

Alk<sup>1</sup> is an optionally substituted aliphatic chain;

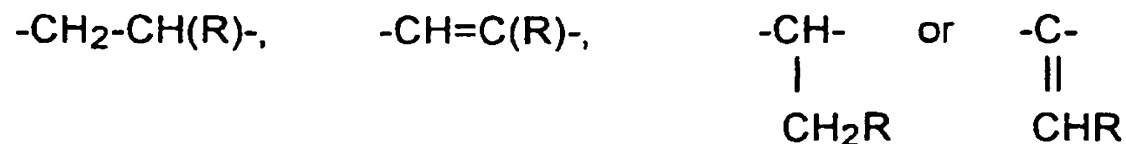
R<sup>3</sup> is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyhetero-

cycloaliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates and *N*-oxides thereof.

2. A compound according to Claim 1 in which R<sup>1</sup> is an α4-integrin binding group.

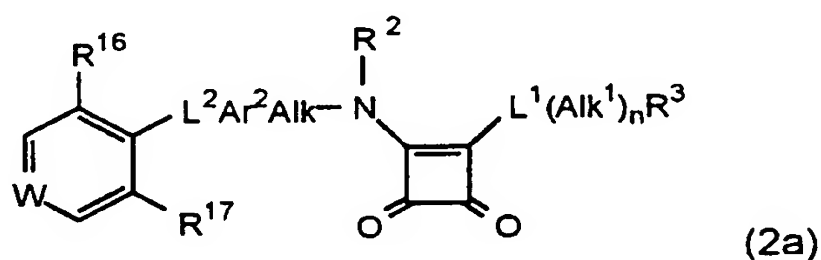
3. A compound according to Claim 1 or Claim 2 in which R<sup>1</sup> is a group of formula Ar<sup>1</sup>L<sup>2</sup>Ar<sup>2</sup>Alk-, where Ar<sup>1</sup> is an optionally substituted aromatic or heteroaromatic group, L<sup>2</sup> is a linker atom or group, Ar<sup>2</sup> is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group and Alk is a chain from:



where R is a carboxylic acid (-CO<sub>2</sub>H) or a derivative or biostere thereof.

4. A compound according to Claim 3 in which Alk is a chain selected from  
-CH<sub>2</sub>-CH(R)-, or  $\begin{array}{c} \text{-CH-} \\ | \\ \text{CH}_2\text{R} \end{array}$
- 5
5. A compound according to Claim 4 in which R is a carboxylic acid (-CO<sub>2</sub>H) group.
- 10
6. A compound according to any one of Claims 3 to 5 in which Ar<sup>2</sup> is an optionally substituted 1,4-phenylene group.
- 15
7. A compound according to any one of Claims 3 to 6 in which Ar<sup>1</sup> is an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group.
- 20
9. A compound according to Claim 8 in which L<sup>2</sup> is a -CON(R<sup>8</sup>)- group where R<sup>8</sup> is a hydrogen atom or an optionally substituted C<sub>1-6</sub>alkyl group.
- 25
10. A compound according to Claim 9 in which R<sup>8</sup> is a hydrogen atom.
11. A compound according to Claim 7 in which Ar<sup>1</sup> is an optionally substituted 2,6-naphthyridinyl and 4-quinazolinyl groups.
- 30
12. A compound according to Claim 11 in which L<sup>2</sup> is an -O- or -N(R<sup>8</sup>)- group where R<sup>8</sup> is a hydrogen atom or an optionally substituted C<sub>1-6</sub>alkyl group.
13. A compound according to Claim 12 in which R<sup>8</sup> is a hydrogen atom.

14. A compound according to any one of Claims 1 to 13 in which  $L^1$  is a  $-N(R^8)-$  group where  $R^8$  is a hydrogen atom or an optionally substituted  $C_{1-6}$ alkyl group.
- 5 15. A compound according to Claim 14 in which  $R^8$  is a hydrogen atom or methyl, ethyl or n-propyl group.
16. A compound according to any one of Claims 1 to 13 in which  $L^1$  is a covalent bond.
- 10 17. A compound according to any one of Claims 1 to 16 in which  $n$  is the integer 1 and  $Alk^1$  is an optionally substituted straight or branched  $C_{1-6}$ alkylene chain.
- 15 18. A compound according to Claim 17 in which  $Alk^1$  is a  $-CH_2-$ ,  $-CH_2CH_2-$ ,  $-CH_2CH_2CH_2-$ ,  $-CH(CH_3)CH_2-$  or  $-C(CH_3)_2CH_2-$  chain.
19. A compound according to Claim 18 in which  $R^3$  is a hydrogen atom.
- 20 20. A compound according to Claim 3 of formula (2a):

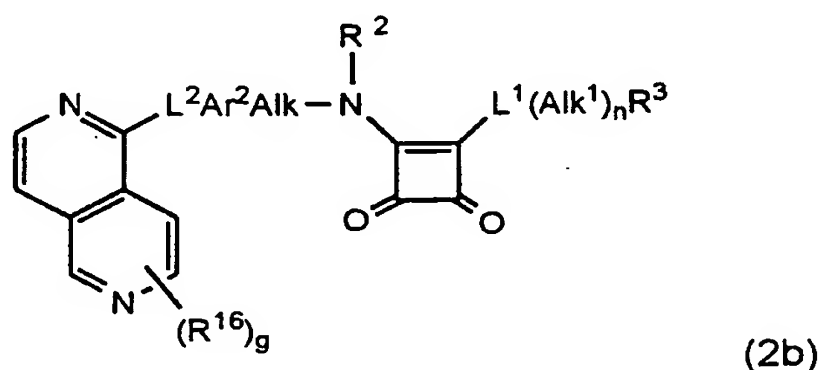


- wherein  $-W=$  is  $-CH=$  or  $-N=$ ;
- 25  $R^{16}$  and  $R^{17}$ , which may be the same or different is each a hydrogen atom or group  $-L^3(Alk^2)_tL^4(R^4)_u$  in which:
- $L^3$  is a covalent bond or a linker atom or group;
- $Alk^2$  is an aliphatic or heteroaliphatic chain;
- $t$  is zero or the integer 1;
- 30  $L^4$  is a covalent bond or a linker atom or group;
- $R^4$  is a hydrogen or halogen atom or a group selected from optionally substituted  $C_{1-6}$ alkyl or  $C_{3-8}$  cycloalkyl,  $-OR^5$  [where  $R^5$  is a hydrogen



atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub> cycloalkyl group], -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>6</sup> [where R<sup>6</sup> is as just defined for R<sup>5</sup> and may be the same or different], -NO<sub>2</sub>, -CN, -CO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -SOR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>R<sup>5</sup>, -OCO<sub>2</sub>R<sup>5</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -OCONR<sup>5</sup>R<sup>6</sup>, -CSNR<sup>5</sup>R<sup>6</sup>, -COR<sup>5</sup>, -OCOR<sup>5</sup>, -N(R<sup>5</sup>)COR<sup>6</sup>, -N(R<sup>5</sup>)CSR<sup>6</sup>, -SO<sub>2</sub>N(R<sup>5</sup>)(R<sup>6</sup>), -N(R<sup>5</sup>)SO<sub>2</sub>R<sup>6</sup>, N(R<sup>5</sup>)CON(R<sup>6</sup>)(R<sup>7</sup>) [where R<sup>7</sup> is a hydrogen atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub>cycloalkyl group], -N(R<sup>5</sup>)CSN(R<sup>6</sup>)(R<sup>7</sup>) or -N(R<sup>5</sup>)SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), provided that when t is zero and each of L<sup>3</sup> and L<sup>4</sup> is a covalent bond then u is the integer 1 and R<sup>4</sup> is other than a hydrogen atom;  
and the salts, solvates, hydrates and N-oxides thereof.

21. A compound according to Claim 3 of formula (2b)



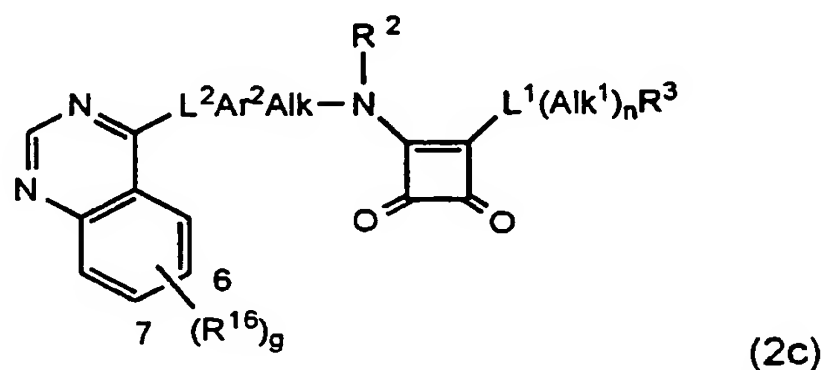
wherein R<sup>16</sup> is a hydrogen atom or a group -L<sup>3</sup>(Alk<sup>2</sup>)<sub>t</sub>L<sup>4</sup>(R<sup>4</sup>)<sub>u</sub> in which L<sup>3</sup> is a covalent bond or a linker atom or group;  
Alk<sup>2</sup> is an aliphatic or heteroaliphatic chain;  
t is zero or the integer 1;  
L<sup>4</sup> is a covalent bond or a linker atom or group;  
R<sup>4</sup> is a hydrogen or halogen atom or a group selected from optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub> cycloalkyl, -OR<sup>5</sup> [where R<sup>5</sup> is a hydrogen atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub> cycloalkyl group], -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>6</sup> [where R<sup>6</sup> is as just defined for R<sup>5</sup> and may be the same or different], -NO<sub>2</sub>, -CN, -CO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -SOR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>R<sup>5</sup>, -OCO<sub>2</sub>R<sup>5</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -OCONR<sup>5</sup>R<sup>6</sup>, -CSNR<sup>5</sup>R<sup>6</sup>, -COR<sup>5</sup>, -OCOR<sup>5</sup>, -N(R<sup>5</sup>)COR<sup>6</sup>, -N(R<sup>5</sup>)CSR<sup>6</sup>, -SO<sub>2</sub>N(R<sup>5</sup>)(R<sup>6</sup>), -N(R<sup>5</sup>)SO<sub>2</sub>R<sup>6</sup>, N(R<sup>5</sup>)CON(R<sup>6</sup>)(R<sup>7</sup>) [where R<sup>7</sup> is a hydrogen atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub>cycloalkyl group], -N(R<sup>5</sup>)CSN(R<sup>6</sup>)(R<sup>7</sup>) or

-N(R<sup>5</sup>)SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), provided that when t is zero and each of L<sup>3</sup> and L<sup>4</sup> is a covalent bond then u is the integer 1 and R<sup>4</sup> is other than a hydrogen atom;

g is zero or the integer 1, 2, 3 or 4;

5 and the salts, solvates, hydrates and N-oxides thereof.

22. A compound according to Claim 3 of formula (2c)



10 wherein R<sup>16</sup> is a hydrogen atom or a group in which L<sup>3</sup> is a covalent bond or a linker atom or group;

Alk<sup>2</sup> is an aliphatic or heteroaliphatic chain;

t is zero or the integer 1;

15 L<sup>4</sup> is a covalent bond or a linker atom or group;

R<sup>4</sup> is a hydrogen or halogen atom or a group selected from optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub> cycloalkyl, -OR<sup>5</sup> [where R<sup>5</sup> is a hydrogen atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub> cycloalkyl group], -SR<sup>5</sup>, -NR<sup>5</sup>R<sup>6</sup> [where R<sup>6</sup> is as just defined for R<sup>5</sup> and may be the same or different], -NO<sub>2</sub>, -CN, -CO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>H, -SOR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SO<sub>3</sub>R<sup>5</sup>, -OCO<sub>2</sub>R<sup>5</sup>, -CONR<sup>5</sup>R<sup>6</sup>, -OCONR<sup>5</sup>R<sup>6</sup>, -CSNR<sup>5</sup>R<sup>6</sup>, -COR<sup>5</sup>, -OCOR<sup>5</sup>, -N(R<sup>5</sup>)COR<sup>6</sup>, -N(R<sup>5</sup>)CSR<sup>6</sup>, -SO<sub>2</sub>N(R<sup>5</sup>)(R<sup>6</sup>), -N(R<sup>5</sup>)SO<sub>2</sub>R<sup>6</sup>, N(R<sup>5</sup>)CON(R<sup>6</sup>)(R<sup>7</sup>) [where R<sup>7</sup> is a hydrogen atom, an optionally substituted C<sub>1-6</sub>alkyl or C<sub>3-8</sub>cycloalkyl group], -N(R<sup>5</sup>)CSN(R<sup>6</sup>)(R<sup>7</sup>) or -N(R<sup>5</sup>)SO<sub>2</sub>N(R<sup>6</sup>)(R<sup>7</sup>), provided that when t is zero and each of L<sup>3</sup> and L<sup>4</sup> is a covalent bond then u is the integer 1 and R<sup>4</sup> is other than a hydrogen atom;

25 g is zero or the integer 1, 2, 3 or 4;

and the salts, solvates, hydrates and N-oxides thereof.

23. A compound which is:
- (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-propylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-2-(2-t-butyl-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(6,7-Dimethoxy-4-quinazolinyl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(6,7-Dimethoxy-4-quinazolinyl)oxy]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(6,7-Methoxy-4-quinazolinyl)amino]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-N,N-dipropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)oxy]phenyl]-2-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-piperidin-1-yl-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (R)-3-[4-(3,5-Dichloro-4-pyridylcarboxamido)phenyl]-3-[(2-N,N-diethylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)oxy]phenyl]-2-[(2-N,N-dipropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- (S)-3-[4-[(2,6-Naphthyridin-1-yl)amino]phenyl]-2-[(2-N,-ethyl-N-isopropylamino-3,4-dioxocyclobut-1-enyl)amino]propanoic acid;
- and the salts, solvates, hydrates and N-oxides thereof.
24. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

# INTERNATIONAL SEARCH REPORT

Intern    1al Application No  
PCT/GB 00/02020

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7    C07C229/36    C07C271/28    C07C229/34    C07C271/22    C07C233/81  
           C07C235/16    C07C235/84    C07C235/64    C07C233/55    C07C255/57  
           C07C235/56    C07C271/58    C07C237/40    C07D295/12    C07D213/81

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7    C07C    C07D    A61K    A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 35855 A (AMERICAN HOME PRODUCTS CORPORATION, USA) 22 June 2000 (2000-06-22) the whole document ---	1-20, 23, 24
A	WO 99 10313 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) cited in the application the whole document ---	1-24
A	WO 98 18460 A (DUGGAN MARK E ; MERCK & CO INC (US); HARTMAN GEORGE D (US)) 7 May 1998 (1998-05-07) cited in the application claims; examples -----	1-24



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

19 October 2000

Date of mailing of the international search report

08/11/2000

Name and mailing address of the ISA

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Authorized officer

Bosma, P

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 00/02020

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>					
IPC 7	C07D213/79	C07D471/04	C07D333/70	C07D239/42	C07D215/42
	C07D239/34	C07D241/42	C07D241/44	C07D217/22	A61K31/122
	A61K31/44	A61K31/505	A61P7/00	A61P29/00	
According to International Patent Classification (IPC) or to both national classification and IPC					
<b>B. FIELDS SEARCHED</b>					
Minimum documentation searched (classification system followed by classification symbols)					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)					
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>					
Date of the actual completion of the international search			Date of mailing of the international search report		
19 October 2000					
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer  Bosma, P		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/GB 00/02020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0035855 55 A		NONE	
WO 9910313 A	04-03-1999	AU 9341998 A EP 1005446 A ZA 9807602 A	16-03-1999 07-06-2000 04-05-1999
WO 9818460 A	07-05-1998	AU 722360 B AU 5239998 A EP 0946165 A US 5952341 A	03-08-2000 22-05-1998 06-10-1999 14-09-1999